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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

SEPTEMBER 1948

THE CLINICAL USE OF RADIOACTIVE IODINE*

SIDNEY C. WERNER, EDITH H. QUIMBY, SC.D.
and CHARLOTTE SCHMIDT, B.A.

It is well known that the thyroid gland takes up iodine.[1] When radioactive isotopes of iodine became available, it appeared reasonable to use this localization for delivery of an internal radiation therapy to the hyperactive gland. As the radioactive atoms disintegrate within the thyroid, they emit beta and gamma rays, producing the same kind of tissue reaction as x-rays, but the irradiation is largely confined to the gland itself.

Two isotopes of iodine are suitable for attempting this type of therapy, I^{130}, with a half life of 12.6 hours, and I^{131}, half life 8 days. The latter was not readily produced until recently, but the former became available in a few localities about 1943, and two groups in Boston employed it for therapeutic purposes in toxic goiter.[2,3] The results of work started about the same time in other clinics have not been reported.

Since the release of isotopes from the atomic energy pile at Oak

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* Presented before the Section on Medicine January 20, 1948.

From the Departments of Medicine and Radiology, Columbia University College of Physicians and Surgeons, and The Presbyterian Hospital, New York City, with the aid of grants from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association and the Lilla Babbitt Hyde Foundation.

Ridge, Tenn., it has been possible for suitably equipped institutions to obtain I^{131}. Accordingly an appraisal of the treatment of toxic goiter with this agent has been undertaken in several hospitals. The study here reported was begun in October 1946; the material is presented as a preliminary report.

Procedure

At the start of the work no adequate basis for dosage planning was available. Decision as to the amount of material to be administered involved taking into account the degree of uptake of the radioactive material by the thyroid gland, and its subsequent release therefrom, as well as of the amount of energy released by the radioactive atoms. Calculations were made as follows: According to theoretical considerations, if a relatively small organ has a uniform concentration of 1 microcurie of I^{131} per gram, and the isotope remains there for total decay, the tissue will receive a radiation dose of about 160 equivalent roentgens.* [4] In the case of the toxic thyroid gland, the iodine gradually leaves the organ at such a rate that the effective dose is reduced to about 120 e.r.

Cases successfully treated with I^{130} in the earlier series mentioned above[2, 3] appear to have received about 2000-4000 e.r. When radiation is delivered more slowly, as with the 8-day isotope, a larger total number of roentgens is necessary to produce the same therapeutic result; accordingly in the present series a dose of 3000-5000 e.r. was made the objective. Assuming a 60-gram thyroid, an uptake of 50 per cent of the administered material, and a gradual loss by elimination from the gland, a dose of about 4 millicuries would be required to deliver this radiation. Treatments were therefore started with this as the amount administered to all cases, although, because of differences in gland size and in iodine uptake, there would be considerable variation in the actual irradiation administered. Thus, an appraisal of clinical response to various doses would be made. This was desirable, since it was not certain whether the calculated dose of radiation was optimal, or whether it should be more or less.

Radioactive iodine was obtained from the atomic energy pile at Oak Ridge, Tenn. After proper standardization and dilution, the material was given by mouth, in water solution, the iodine being carrier-

* The roentgen is the unit for x-rays and gamma rays; it is not at present defined for beta rays. Dosage for these latter is expressed in equivalent roentgens; the ionization produced in air by an equivalent roentgen is the same as that produced by one roentgen of gamma rays, when both are properly measured. The unit is abbreviated e.r.

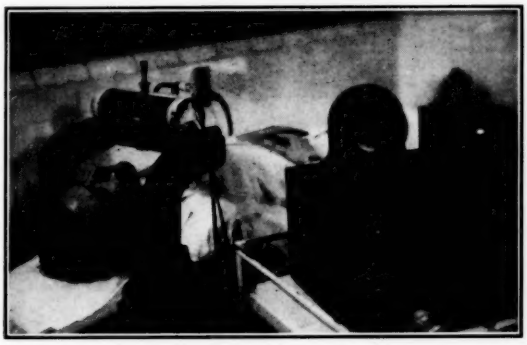

Fig. 1. Patient being measured for radioactive iodine uptake with Geiger counter.

free (i.e., all radioactive). Thus the 4 mc. therapeutic dose contained only about 0.03 micrograms of iodine, which is well below the normal daily intake of the element. In the early cases a tracer dose was not always given in advance of therapy; later this became routine, in order to obtain information about the uptake.

In addition to the therapeutic administration of the material, numerous tracer studies have been made, to determine radioiodine uptake by individuals with normal and diseased thyroid glands. Tracer doses were usually of the order of 50-75 microcuries; the radiation effect on the gland from this amount is considered insignificant.

In both therapy and tracer patients the radioiodine uptake by the gland was measured at different times after ingestion. The patient was placed on a frame as shown in Figure 1, so that the skin over the isthmus of the thyroid was always at 15 cm. distance from the Geiger counter. The first patients were studied from the instant of administration; uptake was followed minute by minute for the first hour, then at 3, 6, 24 and 48 hours. All cases were measured at 24 hours after therapy and weekly thereafter as long as practicable.

Most of the iodine which is not concentrated in the thyroid gland is excreted in the urine, within the first 24 hours. Accordingly urinary iodine output was followed for 24 or 48 hours whenever possible.

The size of the gland was estimated immediately prior to treatment. To aid in this, a series of plasticine models was constructed and their

TABLE I

TABLE SHOWING UPTAKE OF RADIOIODINE BY THYROID GLAND AND URINARY EXCRETION OF THE ISOTOPE IN TRACER STUDIES

Type of Case	*Per Cent in Gland at 24 Hours*			*Per Cent Excreted in 24 Hours*			*Number of Cases*
	Max.	*Min.*	*Aver.*	*Max.*	*Min.*	*Aver.*	
A. Patients without known Thyroid Disorder	36	11	21	76	28	52	30
B. Patients with known Thyroid Disorder							
1. Toxic Goiter							
a. Diffuse	76	44	65	27	6	17	28
b. Nodular	67	33	52		10		7
c. Hyperophthalmic	60	54	58	25	18	22	4
2. Non-toxic Nodular Goiter	24	15	19	data incomplete			3
3. Hypothyroidism	4	1	3	62	48	55	5

Tracer doses were 40 to 100 uc of I^{131} administered by mouth in the form of soluble iodide, carrier free. Uptake measurements *in vivo*, Geiger counter 15 cm. from skin over thyroid.

volumes determined by liquid displacement. They were, for the normal gland, 25 cc., and for the four stages of enlargement, 35, 50, 70 and 100 cc. By palpation it was possible to assign a particular patient's gland to one of these groups, or to a value halfway between two. It is realized that this method is inaccurate, but an approximate knowledge of gland size is essential in evaluating this type of therapy. This lack of accuracy must be kept in mind in connection with any statement regarding dosage.

Radiation dosage was calculated for all treatments according to a formula taking account of millicuries administered, percentage uptake, rate of elimination from the gland, and gland size.[5]

Radioactive Iodine Tracer Studies

The tracer studies were made on normal, hypo- and hyperthyroid individuals as summarized in Table I. The uptake at 24 hours in the normals varied within the relatively narrow range of 15-30 per cent of

the administered amount. In toxic goiter it was over 40 per cent, and in hypothyroidism under 10 per cent. The border regions of 10-15 and 30-40 per cent appear indeterminate. Administration of stable iodine or of anti-thyroid drugs within two weeks prior to the test may vitiate the results.

Urinary excretion in the first 24 hours after radioiodine administration varied from 40 to 70 per cent in the normals and from 10 to 40 per cent in the hyperthyroid cases. The toxic group excreted more of the material in the first 6 hours than in the following 18, probably due to increased renal clearance. In the normals, considerably less appeared in the urine in the first 6 hours than in the remaining 18. Thus the measurement of urinary excretion gives an indication of toxicity, though not as reliable as measurement of gland uptake.

Therapeutic Studies

a) *Type case.* Up to the present time 40 cases of unquestioned toxic goiter, given 47 treatments with I^{131}, have been followed long enough to permit some evaluation of the results of therapy. The follow-up period has ranged from 4 months to more than a year. Fourteen of the patients were men, 26 women. Ages ranged from 23 to 57. Eighteen of the cases were primary toxic goiter not treated previously by any means, whereas 22 were recurrent after operation and had received antithyroid drug therapy for some time without satisfactory relief. All but one case had toxic diffuse goiter; no true hyperophthalmic goiter was treated.

b) *Dosage and Clinical Response.* 1. Millicuries. All cases in this series received from 3 to 4 mc. In the 40 patients treated, there were 13 failures after a single dose of I^{131} and 4 more failures in 7 of these patients given second treatments. Thus 34 of the 40 patients were treated once, and if necessary twice, and have been followed for 4 months or more after therapy. Thirty of these 34 have been put into remission, a case success rate of 88 per cent. The other 6 instances of failure with the first treatment have been retreated too recently to include in this report. On the basis of number of treatments given, there have been 17 failures in 47 treatments, or a treatment success rate of 64 per cent. Four instances of transient hypothyroidism occurred following radioiodine therapy, but these returned to normal within a short time.

2. Microcuries per gram of estimated gland weight. With a rela-

TABLE II

TABLE SHOWING RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT AND DOSE IN MICROCURIES OF I^{131} ADMINISTERED PER GRAM OF ESTIMATED GLAND WEIGHT

	*Number of Treatments**		
uc Adm. per gram	*Success*	*Failure*	*Total*
250	1	0	1
200-250	2	0	2
150-199	9	0	3
100-149	7	2	9
50-99	12	8	20
50	3**	6	9

* Data not available in 3 instances.
** These were all second treatments after failure to respond satisfactorily to the first treatment.

tively constant amount of radioactive material, it is obvious that the larger glands collect much less radioiodine per gram of tissue, and hence receive less actual radiation than the smaller. Therefore, as stated above, estimate of gland size is essential, even though admittedly not accurate, to permit calculation of radiation dosage. The number of microcuries administered per estimated gram of gland tissue is related to the result of treatment as shown in Table II. With doses of 100 or more uc per gram, only 2 of 15 cases failed to respond satisfactorily. With lower doses the successes and failures were equally divided.

The actual irradiation of the gland is the result not simply of the uc administered per gram of tissue, but of the uc retained there. There were no failures in those instances in which more than 75 uc were retained per gram. On the other hand, only one case responded satisfactorily to an initial dose of less than 25 retained uc per gram.

3. *Equivalent Roentgens.* The actual radiation dose in terms of equivalent roentgens depends not only on the uptake by the gland, but also on the subsequent rate of elimination therefrom. Dosages calculated according to the formula allowing for these factors are given in Figure 2, with the corresponding results. There were only 2 failures in 13 treatments of 6000 e.r. or more. In the 3000-6000 e.r. range successes

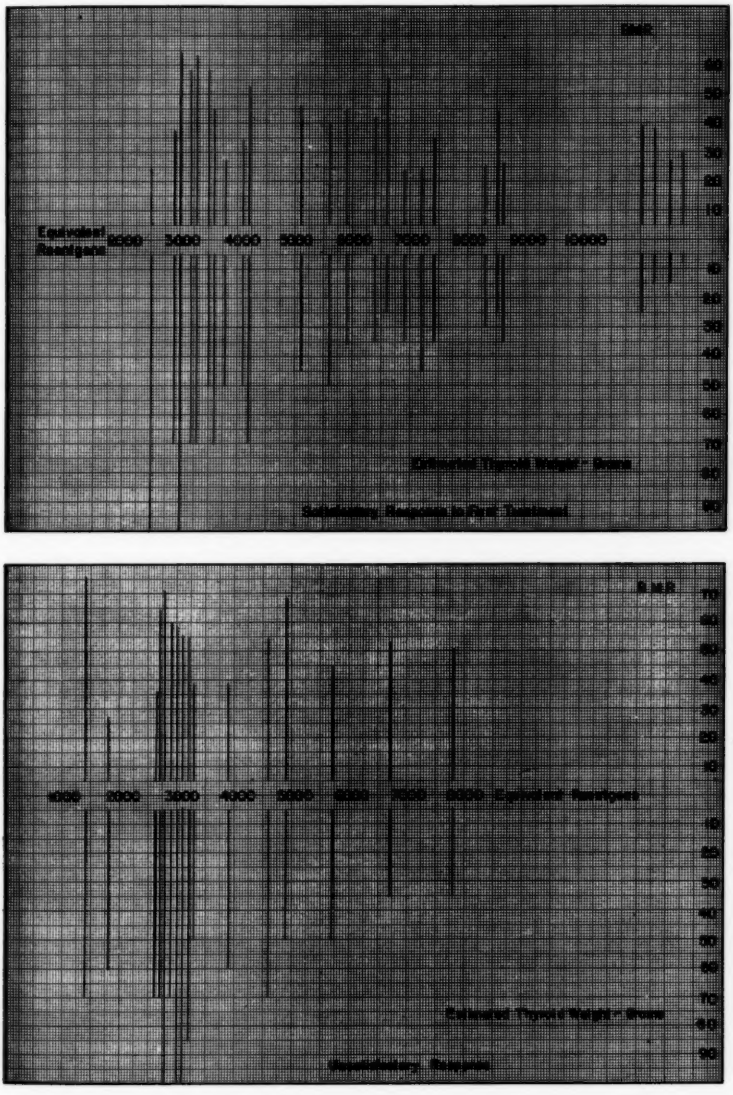

Fig. 2. Chart showing radiation dosage, BMR, and gland size for each individual case. Upper part—successful treatment; lower, unsuccessful. Each patient is represented by two lines, starting at the administered dose of equivalent roentgens. The line extending upward indicates the BMR, the one extending downward, the estimated thyroid weight.

TABLE III

TABLE SHOWING TIME ELAPSING AFTER RADIOIODINE THERAPY BEFORE RETURN OF BASAL METABOLIC RATE TO NORMAL

Months Between Treatment and Establishment of Normal BMR	*Number of Cases**
0-1	2
1-2	12
2-3	10
3-4	5

* Data not available in 1 instance.

and failures were equally distributed. The three successes in the lowest dosage range were repeat treatments after inadequate initial responses. The four instances of transient hypothyroidism mentioned above occurred with doses of 2900, 6900, 7400, and 8600 e.r.

c) *Further Analysis of Failure of Treatment.* The factors influencing radiation dosage, as has been stated, are the amount of radioactive material administered, the weight of the thyroid gland, the percentage retained in the gland and the rate of its release. The pre-treatment level of the basal metabolic rate may also be significant. In an attempt to visualize the importance of some of these factors, Figure 2 is presented, to show, for each individual case the gland size, pre-treatment BMR, and dose in equivalent roentgens. This dose takes account of uptake and elimination. The upper half of the figure deals with the successful treatments, the lower with the failures.

As would be expected, most of the failures are in the low dosage region, in which are the large glands. The reason for failure in the three or four cases receiving apparently adequate doses is not clear. Possibly the glands were larger than estimated, which would mean that the radiation doses were smaller than indicated. It may be noted that on the whole the failures show higher basal metabolic rates than the successes.

It is interesting to observe that there are a number of successes in the lower dosage region, which, in this series, means large glands. On the average these successful cases have lower BMR's but this is not always the case. There is apparently an actual region of overlap in dosage

for successful and unsuccessful therapy. It is important to increase the series and to treat large glands with radiation doses of the same magnitude as those received by the smaller ones.

d) *Time Necessary for BMR to Return to Normal.* Although a few successfully treated cases experienced a return in basal metabolic rate to normal in less than 2 months, most of the cases were not in remission until the end of the second or middle of the third month. A few required even longer (Table III).

e) *Complications.* The incidence of complications resulting from radioiodine therapy is not high.

1. Hypothyroidism. Four instances of transient hypothyroidism occurred with I^{131} doses of 3 to 4 mc.; these patients received radiation doses of 2900, 6900, 7400, and 8600 e.r. The symptoms and signs of hypothyroidism were noted in the third to fourth month after treatment, and cleared within the space of a month, with one exception, which required somewhat longer.

2. Sore throat and cough. A persistent sensation of a head cold or sore throat occurred in 6 instances with a hacking cough, and in one other, cough alone, without adequate evidence of an upper respiratory infection to account for it. This appeared several weeks after treatment and subsided about a month later.

3. Tender gland. Marked tenderness of the thyroid gland to palpation was noted in 2 cases, subsiding after several months. The glands became indurated; this characteristic was noted in many cases without associated tenderness.

4. Flare-up of toxicity. Three instances of increased toxicity in the month following therapy were noted. This brought the basal to about 15 per cent higher than before therapy, and was sufficient to create alarm concerning the patient's status, though fortunately neither cardiac failure nor thyroid storm was precipitated in any instance.

5. Radiation sickness. No instance of this complication was noted.

6. Intercurrent pregnancy. Two patients were unwittingly treated in the first 2 months of pregnancy. No apparent harm to patient or fetus has been evident.

f) *Reduction in Gland Size.* In most cases the glands were reduced to within normal limits or less by 3 months following therapy, when remission was obtained. In the instances of failure of therapy, gland size was somewhat reduced, although not to normal limits.

g) *Radiation Hazards.* Two aspects of radiation hazards must be considered, the danger to the patient and to other individuals.

1. Danger to the patient. This might be either immediate or late. The analysis of complications just made indicates that there is no immediate danger to the patient from the effects of radiation. The possibility of late radiation damage leading to malignant change cannot be ignored. However, a calculation of radiation dosage administered to many individuals in intensive x-ray therapy of the neck, and comparison with the doses in this series, indicate that the hazard is not great.

h) *Later Malignancy.* A concensus of opinion based on experience with x-ray treatment of toxic goiter indicates that later malignant complications from radioiodine therapy are also probably unlikely.

Discussion and Conclusions. Radioactive iodine, half life 8 days, has been used 47 times in the treatment of the 40 cases of hyperthyroidism at the Presbyterian Hospital included in this report. Twenty-seven of these responded favorably to a single dose. Seven of the 13 failures with one dose were given a second treatment and 3 more responded favorably; the remaining 6 cases have been retreated too recently to report. Thus of the 34 cases given a single dose, and when necessary a second, 30 were put into remission (88 per cent) as judged by a follow-up period of 4 months or more. This success rate is especially striking since half the cases were recurrent toxic goiter after operation, and were uncontrollable by other methods of therapy. The series is small as yet, and further data are necessary before a final evaluation of the method can be made.

The factors pertaining to the failure of therapy have been discussed. It appears that when an adequate amount of radioiodine is administered, as determined by the percentage uptake and the size of the gland, a relatively high percentage of successes should be expected. A dose of 100-150 uc per gram of thyroid weight administered, or of 50-75 uc per gram retained seems adequate. A radiation dose of about 6000 equivalent roentgens appears to be the desirable level. The problem, of course, is to select a dosage which will control the toxicity, but not induce gland underfunction and permanent hypothyroidism.

The success rate here reported compares well with that of surgery (90 per cent) and surpasses the results of x-ray therapy (80 per cent) and of thiouracil and propyl thiouracil treatment (about 60 per cent in primary goiter, 10 per cent in recurrent goiter).[6] Surgery provides relief

in a shorter time than the two or three months usually needed to induce remission with radioiodine, but has the objections attendant on operation. Antithyroid drug therapy may take one or two years, without assurance of success, but has few complications, and little question of cancer formation later. In view of the remote chance of late malignancy following radioiodine therapy, most workers in this field agree that such therapy is still too new for general use, and that it should be employed only in those centers where adequate follow-up is available, where careful measurements of dosage can be carried out, and where strict precautions against radiation hazards from the handling of the iodine can be maintained.

Complications have not been severe and no instance of permanent hypothyroidism occurred in the present series. The presence of cardiac failure, a rare event nowadays, may be a complication prior to radioiodine treatment preventing its immediate use, due to the uncertain success which follows a single dose and to the 3 months interval until success or failure can be determined. However, even with failure, the patients are usually greatly improved. Finally, malignant exophthalmos has not occurred in this series. However, if the mass of gland tissue is a factor in inhibiting the appearance of this condition, the destruction of gland tissue by radioiodine contraindicates its use where this is a likely possibility. This point remains to be settled.

Summary

1. Radioactive iodine of 8-day half life, I^{131}, has been used in tracer studies of iodine uptake by normal and disordered thyroid glands, and in the treatment of 40 cases of toxic goiter.

2. Tracer uptake has diagnostic value, when stable iodine or antithyroid drugs have not been given shortly before this procedure. Normal uptake is 20-30 per cent of the administered tracer dose of 50-75 uc. Anything more than 40 per cent is regarded as definitely hyperthyroid, anything less than 10 per cent as hypothyroid.

3. Therapy has been successful in 30 of 34 cases after one, or when necessary two doses, with four failures. Six other treated cases did not respond to one dose, and have not been followed after a second long enough to draw conclusions.

4. The causes of failure in the present series have been analyzed; they appear to be due to inadequate dosage, related mainly to the size

of the gland. It is possible that an unusually high basal metabolic rate may also contribute to an unsatisfactory result.

5. The complications following radioiodine therapy include sore throat, cough, tender gland, flare-up of toxicity, and transient hypothyroidism. Only a few cases of each have been observed; none of them was serious.

6. Radiation hazards attendant on this therapy are analyzed; under the present conditions they are unimportant.

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THE ORGANIZATION OF CARDIOVASCULAR FUNCTION*

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THE FUNCTION OF THE CARDIOVASCULAR SYSTEM

THE IMMEDIATE environment of the cells in lower organisms varies with remote changes over which the organism has no control. In multicellular organisms, however, the situation is different; the cells are bathed in a fluid which tends to resist the commonly occurring environmental changes because of the character of its physical and chemical properties.

In the larger metazoa the importance of a stable environment for the cells is so great that mechanisms have developed which provide for a constant renewal of the intercellular fluid. In man this is accomplished by the continuous filtration of fluid from the blood stream into the extravascular spaces and its return by way of the capillaries and lymphatics.

Apparently the complexity of the cardiovascular system has evolved in response to the difficulty of providing a proper amount of fresh fluid to the tissues and to the organism's dependence on the adequacy of this provision. The prime function of the cardiovascular system, therefore, is to assure a rapid turnover of tissue fluid in amounts adapted to the activity of the various parts of the body.

A brief review of the general mode of operation of the cardiovascular system should consider first the formation of tissue fluid.[1] An unselected fluid of low protein content is filtered from the blood partly through the endothelial cells of the capillaries and partly through the cement substance which joins them. The rate of filtration depends on the pressure within the capillary, on the permeability of its wall and on the forces tending to oppose the extravasation of fluid. This fluid is

* Based on two of a series of three lectures delivered at New York University, December, 1946.

normally returned to the blood by a force resulting from the pressure in the tissue spaces and the osmotic pressure of the proteins remaining in the plasma. Some components of extravascular fluid, especially protein and particulate matter, return by way of the lymphatics.

To serve these ends are the capillaries—thin-walled tubes whose patency varies with the rate of metabolic activity of the tissues which they supply. The pressure within the capillaries forces the blood on through the venules into the great veins and so to the heart. The continual movement of the structures in which the veins are embedded helps to move the blood forward since it is prevented from returning by the arrangement of the valves. Thus the veins are continuously emptied and the outflow from the capillaries is facilitated.

All the blood which is returned to the heart is pumped through the pulmonary circuit and then expelled into the aorta which being elastic serves as a reservoir to contain at all times enough blood under pressure to supply the demands of the tissues. The long arteries deliver the blood to various organs; there the arterioles serve as shutoff valves which maintain the blood pressure since they relax only enough to deliver the blood immediately required by the tissue in which they lie.

The central feature in the mechanism for assuring a turnover of tissue fluid adequate to maintain a constant environment in regions of active metabolism is the fitness of the cardiovascular system to deliver a large amount of blood at high pressure.

The usual description of the circulation presents the heart and medulla oblongata as directing the cardiovascular system to supply blood where and when it is needed; the physical, endocrine and higher nervous aspects of cardiovascular regulation being interesting addenda to the main story.

The chief intent of this lecture is to consider the cardiovascular system from a different point of view. The cardiovascular system will be treated as a mechanism on which *each tissue may make demands that will be automatically supplied* within the limitations of the system. The system is self-adjusting and self-compensating for the ordinary loads put upon it through a combination of physical, chemical, and medullary reflex controls. The hypothalamus biases or guides these automatic adjustments in such a way as to integrate the requirements of various body functions and to provide for special needs related to changes in the external environment. All of these adjustments are to a greater or lesser

degree subject to modification by endocrine activities called into play by common emergencies.

A brief review of the history of our knowledge of the cardiovascular system will show how the heart came to be erroneously considered as the master of the circulation and why only recently attention has been focused on the capillary which is the true functional center of the cardiovascular system.

Historical Review

From the earliest times the heart has been correctly recognized as of supreme importance. Men observed the presence of the apex beat in the chest and its cessation at death; the dramatic and usually fatal results of wounds involving the heart further accentuated its importance.

The foundation of modern analytical physiology was laid in 1628 with the publication of Harvey's book, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*.[2] The title, together with the evidence presented, still further accentuated the central importance of the heart. Thus enthroned, the heart ruled our concepts of the cardiovascular system with a progressively heavier hand until well into the present century. Harvey recognized that the blood in the arteries is under pressure (Chapter 3) and that the quantity of blood expelled by the heart varies from time to time (Chapter 9). He promised to report measurements on cardiac output but this promise was never fulfilled nor have any notes of such experiments been found. We are now beginning to recognize that these two measurements—blood pressure and cardiac output—are necessary for a rational understanding of the behavior of any particular heart.

Soon after Harvey's publication, the early microscopists described the capillary bed without apparently realizing that this was much more than the link in the chain which completes the circulation. The next dramatic advance in our knowledge of the physiology of the cardiovascular system was the publication of Stephen Hales' work on hemostatics[3] which gave the first measurements of blood pressure and described its pulsations and their relationship to the heart beat. Here again the accident of experimentation continued to place emphasis upon the heart.

During the early nineteenth century the recognition at autopsy of hearts grossly enlarged by dilatation or hypertrophy and their relation-

ship to what we now recognize as heart disease on the one hand and Bright's disease[4] and essential hypertension on the other continued to keep the emphasis where it had been before.

This emphasis led Fick[5] in 1870 to explore the relationships now known as the Fick principle and to point out that if quantitative experimental techniques were available it would be possible to determine the cardiac output accurately from the oxygen utilization of the whole organism and the difference in oxygen content between the arterial and venous blood. It was some years before the Fick principle was used for the determination of cardiac output in experimental animals and it is only quite recently that it has come to a full fruition with the development of the techniques which make it applicable to man. The practical value of the Fick method of measuring cardiac output in man seems to have diverted attention from the very important theoretical implications of the Fick principle.

In the middle and later parts of the nineteenth century, physiologists showed great experimental ingenuity and skill in the design and construction of instruments for the registration of small mechanical changes. Their techniques, the new availability of anesthetics and the increased number of persons trained and interested in technical procedures which followed the industrial revolution combined to stimulate research. All phases of physiology underwent a rapid increase in the rate of accumulation of factual knowledge; and because of the mechanical techniques available, this knowledge in the field of cardiovascular physiology was directed mainly to the heart and great vessels since these structures are large and readily accessible.

At the turn of the century, when Riva-Rocci[6] introduced the sphygmomanometer, the accumulated information about arterial blood pressure, obtained mainly from anesthetized animals, became directly available for use in clinical medicine. The electrocardiograph which readily gives the clinician information about the heart, precise to thousandths of a volt and hundredths of a second, still further spotlighted the heart.

The pioneer studies of Elliott[7] on the vascular properties of extracts of the adrenal medulla and those of Dale[8] and of Kamm[9] on the pressor principle from the pituitary body provided the factual beginnings for our present views of the endocrine control of the cardiovascular system.

In the light of this historical review it is understandable that the cir-

culation came to be thought of as a heart and arteries, which, under the control of the medulla, forced blood at pressures determined by the vasomotor centers through arterioles into capillaries whose state of dilatation is to some extent controlled by local metabolism.

Knowledge has also accumulated about a variety of other phenomena in cardiovascular physiology. These include reflexes controlling the circulation, endocrine substances which affect the arterial blood pressure, the influence of pain, emotional excitement and other states transmitted from the higher centers to the cardiovascular system, as well as the behavior of the system in response to various emergencies such as shock, hemorrhage, violent exercise and extremes of heat and cold. As might be expected attention was focused on the heart and great blood vessels which were easily accessible to study rather than on the peripheral circulation and capillaries which are the principal reason for the existence of the cardiovascular system.

During the first quarter of this century Starling[10] isolated first the heart and then the heart and its connections with the medulla from the rest of the cardiovascular and nervous systems. It then became evident that the heart and its immediate connections were so organized that, within wide limits, this system would expel as much blood as came to it by the veins against whatever pressure obtained in the aorta.

This self-regulating system consists of the heart (including myocardium, conduction system, and coronary circulation), the medulla oblongata and the reflex circuits from the great veins, pulmonary arteries, aortic arch and carotid bifurcations, which pass through the medulla and back to the heart by way of the vagus and sympathetic nerves. Starling emphasized that there was nothing within the heart and its nervous connections which determined the work which it would do either in point of quantity of output or of pressure, but that the activity of the heart and its accessories was determined from without by the demands of the other parts of the body, as expressed by the venous return and the aortic tension.

This *dethronement* of the heart from the position which it had occupied in the minds of most writers as the central determiner of the circulation was so radical that its full significance has been accepted only very slowly by physiologists. Those who have devoted critical attention to clinical cardiology have had an even harder time than the physiologists in convincing their colleagues of the necessity of recog-

nizing that the behavior of the heart is determined by the demands made upon it and that the heart does not determine the activity of the peripheral circulation except in cardiac failure.

Damage to the heart, mild or severe, acute or chronic, chemical or biological, gives signs in the peripheral circulatory system only when the load put upon the heart is so great that the damaged heart can no longer sustain the load and begins to fail. In Stokes-Adams syndrome the cardiac arrest causes a complete failure of the heart to pass the blood on to the arterial system so there is a fall in blood pressure and syncope. In congestive heart failure, even in its earliest stages, the presence of edema, dyspnea and other effects of raised venous pressure suggests that the heart is failing to remove all the blood from the veins.

If we consider earlier stages of those processes in the myocardium which ultimately lead to failure we find little evidence that mild impairment of the heart affects the delivery of blood to the tissues, for there is no change in blood pressure nor in resting cardiac output. It is true that the cardiac reserve is impaired; whereas a normal heart may respond to violent exercise by a nine-fold increase in output even against a raised aortic blood pressure, a slightly damaged heart will show signs of failure to sustain the extra load of moderate exertion. Ordinarily in patients with conduction defects or errors of rhythm shown solely by the electrocardiogram, this failure to meet an extra demand is demonstrable only when the cardiovascular system is subjected to severe stress. In many acute coronary attacks, however, the blood pressure falls rapidly during the first hours or days; the decline of blood pressure is said to be due to the weakness of the myocardium. This explanation is probably true in severe coronary attacks but in minor attacks the fall of blood pressure may be due in part to a combination of the relaxation of the arterial system from the diminution of the pain and from the influence of the sedatives used, and to the fact that the enforced sedation and rest have so lowered the tissue demands for blood that the blood pressure falls rather for lack of demand than because of lack of available driving force.

One still hears of a pulse acceleration speeding the circulation or making the heart work harder, or of the force of the heartbeat determining the arterial blood pressure. Starling, on the contrary, showed that increased force of beat is due to raised aortic pressure. Similarly, when the total blood flow and aortic pressure are so great that the heart

might be faced with an inordinate amount of work per beat, we see the Bainbridge accelerator reflex in operation. This causes the heart to beat more frequently when there is more work to do. Acceleration by itself probably affects the venous return, the cardiac output (minute volume) or the arterial blood pressure chiefly when the heart is close to physiological failure.

During the 19th century the details of the peripheral circulation were receiving considerable attention. One may mention only such highlights as the many studies of various aspects of vasomotor control; the work of Gaskell[11] who saw the local dilating effects of metabolites but failed to establish for this discovery the importance it now has; and Starling's description of the formation of tissue fluid and the nature of its demands on the capillary circulation. Details of the behavior of the capillaries and their adaptation to the demands for tissue fluid were elucidated largely after the turn of the 20th century by the work of August Krogh[12] and by the studies of Sir Thomas Lewis[13] upon the minute vessels of the human skin. More recently this work has been extended by Chambers and his collaborators.[14] The physiology of the capillaries and of tissue fluid formation now appears to be receiving the attention which it deserves.

The cardiovascular system is still commonly visualized as a heart and arteries, which, under the control of the medulla, force blood at pressures determined by the vasomotor centers through arterioles into capillaries whose state of dilatation is to some extent controlled by local metabolism. After giving rise to tissue fluid this blood is returned by the veins to complete the circulation.

It seems possible at this time to improve our general understanding of the circulation by considering, first, the supply of blood to the capillaries in response to local demands; secondly, the endocrine mechanisms which integrate cardiovascular activity to meet stereotyped emergency situations; thirdly, the self-regulating arrangements whereby the medulla, heart, and great vessels work together in a self-compensating fashion to provide a continuous and almost inexhaustible reservoir of arterial blood at high pressure; and finally, to consider those phylogenetically recent and individually acquired mechanisms whereby unexpected external events and emotional states may make appropriate modifications in the behavior of the cardiovascular system.

Physical Regulation of Cardiovascular Function

The regulation of the cardiovascular function, that is, the adaptation of its various parts to momentary changes in the internal and external environments, like the regulation of many other important physiological functions, seems to depend basically upon the physical structure of the system and the effect on it of physical changes in the environment. It is this basic automatic physical regulation that the chemical and nervous mechanisms modify. For this reason the physical aspects should be first considered. Since the knowledge of cardiovascular physics is still very patchy, a few illustrative examples of these physical considerations must suffice.

Capillaries: In all organisms a rise of temperature, whether transmitted from without or generated within, is accompanied by an increase in metabolic rate and in the diffusion currents by which the metabolic needs are satisfied. In the mammal the arteriole and capillary are the keys to the turnover of tissue fluid and thus to the constancy of the internal environment. These structures relax when the temperature around them increases and thus allow more blood to flow to the warmed part. This is true whether the warmth is due to increased metabolic activity of the cells in the neighborhood, or, as in the case of the skin, to warmth from without.

The result of mechanical stimulation is another interesting example of the physical regulation of the circulation. In nature a mechanical stimulus is the warning or actual forerunner of impending injury and the vasoconstriction which it produces may sometimes serve to diminish the loss of blood. This vasoconstriction from mechanical stimulus is a well-known laboratory phenomenon and may be observed in arteries, veins, and in the capillaries of the skin. The development of other and presumably more effective chemical and nervous reactions to injury has masked this reaction so that in man at present it appears to be somewhat vestigial, but we should remember Barcroft's[15] warning against dismissing observations whose meaning is obscure. "Accidents happen in nature as elsewhere, but—I range myself on the side of those that regard a phenomenon as more likely to have a significance than not. Those who think with me must shoulder the burden of discovering what the significance may be, but on our opponents rests the much heavier burden of proving the phenomenon to be an accident if indeed it be such."

Some other examples of the physical regulation of the circulation may be found in the physiology of the veins, the heart, the pericardium, the great arteries and the blood.

Veins: The respiratory pump and the massaging action of the muscles are the best known of all the physical means of modifying the venous return in accordance with the metabolic activity.

Heart: Starling's law[16] suggests that the fundamental structure of the heart is responsible for adjusting its activity in response to the physical effect of distension, and so adapting the amount of energy produced to the work necessary to maintain the circulation of the blood coming to the heart. Cardiac muscle, like skeletal muscle, is so constructed that a physical condition (the length and tension of the fibers) determines the amount of energy which will be released at its next contraction. The diastolic volume of the ventricle is determined principally by the arterial tension at the end of the previous systole and by the venous return during diastole. In this way, since the factors determining the work of the heart determine also its volume at the end of diastole, the energy discharge in systole is automatically regulated in accordance with the amount of work to be done.

All muscles have such a mechanism for adjusting their activity to the work they must do. In the case of the heart, however, the Bainbridge accelerator reflex further extends the ability of the organ to accept increased loads without failure. The venous return and the aortic pressure set the task for the heart. These factors adjust the heart's ability to perform the task by the means just discussed.

Pericardium: The principal function of the pericardium is to set a physical limit to the stretching of the heart and thereby to minimize the chances of functional valvular incompetence and muscular rupture. Yas Kuno[17] concluded that the pericardium does in fact restrain venous filling. He found that slitting the pericardium increased not only the maximum diastolic volume but also the maximum work output obtainable from a heart-lung preparation. Wilson and Meek,[18] using an X-ray method and thus avoiding the use of the open-chest preparation, confirmed this conclusion.

Windkessel: The great arteries or windkessel are primarily concerned with the acceptance of the systolic discharge of blood and its delivery to the tissues during diastole. Evidence is accumulating that its capacity and rigidity may change rapidly in a direction which tends

toward the preservation of the *status quo*. The mechanism of this change is disputed. As the blood pressure rises, the windkessel becomes more rigid and thus resists further distension. This is to be expected from the elastic behavior of many similar structures. The question at issue is whether or not there is a specific mechanism for rapidly changing the elastic properties of this structure comparable with the elastic changes seen in muscular contraction.

Any non-rigid container can accommodate to additions to its contents by stretching in response to an increased internal pressure. The relationship between the pressure applied and the increase in capacity or between the stress and the strain may be plotted. The result represents the elastic property of the structure. With a few exceptions, which the physicists refer to as "perfectly elastic bodies," such a graph is a curve indicating that within limits the more a structure is stretched the more difficult it is to stretch it further. This property is recognized beyond doubt in the aorta just as in other tissues. Skeletal muscle and probably other muscles also are characterized by the fact that this elastic curve for relaxed muscle differs importantly from that for contracted muscle. There has been some controversy as to whether the aorta, like muscle, can exhibit such rapid changes in its elastic properties.

Wiggers and Wégria[19] recorded the simultaneous changes in aortic pressure and aortic diameter of dogs subjected to acute pressor effects of epinephrine, pitressin, "vagus stimulation" and asphyxia. In each case, as the pressure rose the aorta first expanded, then shrank, and finally exhibited an increased distensibility. This is exactly what would be expected if the aorta were a vessel of pure muscle and responded to the rise of pressure by contraction and to the subsequent fall by relaxation. Exact analysis of the data is difficult since there is a slight lag in the aortic response, but the above interpretation of the findings is in essential agreement with Wiggers.

Blood: The inherent homeostatic nature of blood was most completely presented in L. J. Henderson's book[20] "Blood, a Study in General Physiology" which J. S. Haldane[21] aptly discussed as "Blood, a Study in Physical Chemistry." Blood, even on the more strictly physical side, is a remarkably "self-regulating" fluid as is illustrated by the effects of changing blood viscosity. The principal variation in viscosity is due to changing red cell count. One of the important consequences of this is that anemic blood, which carries less oxygen per cubic centimeter

than normal blood, can pass more easily through the vascular system because of its lowered viscosity, and thus deliver more oxygen per minute than it otherwise would.

These examples show that much of the organization and regulation of the cardiovascular system is inherent in the physical character of its ingenious structural arrangements.

Chemical Regulation of Cardiovascular Function

The control of the distribution of blood is mainly by chemicals produced by the tissues concerned. The essential relationship of these substances to blood distribution is often overlooked. The chemicals now under discussion are quite distinct from the hormones and for convenience of discussion we may make an incomplete separation between those whose cardiovascular actions occur near their site of production and those whose action is central or general.

Chemicals with Local Action: Gaskell[11] in 1877 was the first to recognize the vasodilator properties of the acid products of metabolism and their importance in increasing the blood flow through active tissues. Half a century later a revival of interest in this subject led to its study by newer methods in many laboratories. Anrep,[22] summarizing the work to which he and his colleagues so largely contributed, showed clearly the quantitative connection between the activity of a tissue, its ability to alter the composition of the blood flowing through it, and the rapidity of its blood flow. Blood collected from an active limb and then perfused through a resting limb consistently increased the blood flow. This was a complete quantitative establishment of the concept that the chemical products of metabolism control the flow of blood; moreover, muscular activity produces a greater blood flow than does ischemia. Anrep was inclined to attribute the greater part of this effect to histamine. Excess carbon dioxide or lack of oxygen could be made to imitate the "activity" effect both in intensity and time scale, but either a lack of oxygen or an excess of carbon dioxide was invariably accompanied by an excess of histamine in the venous blood.

The specific products of metabolism which are known to be vasodilators include hydrogen-ion, carbon dioxide, lactate-ion, phosphate, adenosine and related compounds[23] and histamine. To these metabolites may be added diminished oxygen tension.

A large literature on the vasodilator properties of each of these

metabolites indicates uncertainty as to their efficacy in the concentrations which may be expected at the actual site of production. Acidity, histamine, and adenosine triphosphate, however, are strong vasodilators and are probably effective even in the concentrations involved in mild activity, especially if reinforced by carbon dioxide and lactates.

The rise in hydrogen-ion concentration which occurs in active tissues breaks down an inactive compound liberating kallikrein which further adds to the accumulating vasodilator environment.[24]

A sufficient accumulation of metabolites can produce a maximal blood flow of a magnitude quite different from the increases produced by the nervous system, by acetylcholine (which is abundantly liberated in an active muscle), or by the ergotoxine-epinephrine sequence.

Much more investigation is needed to elucidate the relationships and relative importance of these various vasodilator influences; but it is quite clear that locally liberated chemicals provide, for any tissue that becomes active, a large increase of blood supply. This depends only upon an adequate reserve of arterial blood at a sufficient pressure and is independent of specific nervous or endocrine regulation.

There are many other vasoconstrictor and vasodilator substances extractible from blood and tissues which have not been sufficiently studied to enable us to distinguish between the pharmacological accidents of the extraction process and substances which may have physiological meaning.

Chemicals with General Action: Carbon dioxide is one of the most interesting and controversial chemicals from the cardiovascular point of view. This substance probably acts locally at its point of generation, as do other metabolites, to produce vasodilation and increased local blood flow; but as the blood bearing this excess carbon dioxide passes into the arterial system it acts centrally and may produce a generalized vasoconstriction. This state of vasoconstriction tends to divert the blood from regions which are not actively metabolizing to those which are, and at the same time tends to maintain or even elevate the blood pressure in the face of the extra drain produced by the metabolic requirements of the active region. This central vasoconstrictor action of carbon dioxide is, in part at least, a reflex originating from the aortic and carotid bodies. Carbon dioxide in the blood stream has further effects upon the heart rate and the coronary system. These effects are fairly well described, but their importance in the integration of cardiovascular activity with

the activity of the tissue producing the carbon dioxide needs further clarification.

Because it is the best known, carbon dioxide has been taken as the chief example of the substances which act usefully at a distance from the site of their origin but fail to fit into the usual concept of hormones. Further, it illustrates a common and paradoxically useful occurrence. Where carbon dioxide causes local vasodilation and general vasoconstriction, two diametrically opposite mechanisms work toward the same end—that is, more blood flow to the site of production of carbon dioxide.

The lactate-ion provides another useful illustration of the chemical integration of the cardiovascular system. As a vasodilator[11] produced during muscular activity, it makes an extra demand on the heart. If produced in sufficient amount significantly to raise the lactate content of arterial blood, it provides a readily available fuel for the heart.

The chemical regulation just discussed serves to ensure that each part get a blood supply in accord with its activity. The complexity of the organism, however, is such that an excessive demand made simultaneously by two different organs might cause a breakdown of the whole system. One organ even might so tax the system that some vitally and immediately important function would not be properly served.

Endocrine Integration of Cardiovascular Function

The chemical and physical controls of local origin are therefore in a sense anarchistic. If many tissues simultaneously become active and by their local mechanisms preempt a large blood supply, the demands may exceed the capacity of the cardiovascular system; but endocrine and nervous mechanisms regulate the parts of the cardiovascular system so that they continue to function harmoniously even in the presence of extreme demand. These mechanisms so integrate the blood supply to different parts of the body that non-essential functions shall not dangerously divert blood from essential or emergency functions. The maintenance of harmony within the cardiovascular system seems to be mainly a medullary function; the adjustment of cardiovascular activity to the needs of different parts of the body and to external events is mainly handled by endocrine means and by the higher parts of the brain.

Certain emergencies such as trauma, shortage of water or minerals, or the need for sudden exertion recur frequently in the history of an

individual or species. These emergencies seem to excite endocrine mechanisms which integrate the local demands with requirements of the whole organism.

The Renin Mechanism: A variety of frequent natural accidents which occur in all species and threaten life produce a diminution of pulse pressure, a rapid pulse rate and a diminished plasma volume. In such conditions, as for instance hemorrhage and shock, the threat to life is tissue anoxia. Since the circulating blood volume may become too small to fill the vascular system, the heart is inadequately filled, the cardiac output drops and the blood pressure falls to a level where it fails to force enough blood through the coronary and cerebral blood vessels to sustain life. In these disastrous states where death is imminent, all the available mechanisms—physical, endocrine, and nervous—come into play to maintain the failing circulation.

Here, however, I wish to analyze the first minor deviations from the normal physiological state and the mechanisms which are usually successful in counteracting them. In trauma, pain accelerates the heart and by sympathetic excitation tends to diminish the lumen of the renal arteries. Loss of blood—either by external hemorrhage, bleeding into dilated capillaries, or excessive transudation of fluid through the capillary walls —tends to diminish the systolic output both by defective diastolic filling and by reflex cardiac acceleration. So, on many counts, we may expect the force of the pulsations delivered to the renal parenchyma to be diminished. This diminution, perhaps by interfering with the normal expansile pulsation of the kidney[25] is followed by an immediate liberation of renin into the blood stream. The delay in this reaction is probably negligible, for the liberation of renin has been demonstrated within four minutes of the stimulus.[26] Probably the change in pulse pressure necessary to produce an effect is very small.[27] If the amount of renin liberated is small, the most striking effect is a constriction of the efferent glomerular vessels of the kidney.[28] This increases the fraction of plasma filtered off by the glomerulus and thus enables the elimination of soluble wastes to be maintained even though the blood flow through the kidneys is diminished. A somewhat larger liberation of renin causes a more generalized vasoconstriction together with splenic and venous contraction, and perhaps, also, a cardiotonic effect. All these effects tend to prevent the blood pressure from falling as the effective blood volume diminishes. That this mechanism fails in fatal shock and hemorrhage

through exhaustion of the renin-substrate[29] and probably, also, through exhaustion of the kidney,[30] is perhaps evidence that it has been useful in the minor and non-lethal disturbances.

That renin may, in fact, be liberated promptly by a normal kidney and may contribute to vascular homeostasis is based securely on a wide variety of experiments.

The anesthetized animal's blood pressure will rise within fifteen minutes of appropriate interference with its renal blood supply. This has been shown to be due to the release of renin.[31] Hemorrhage or injection of Nembutal[26, 27] will cause the immediate liberation of renin.

The intimate nature of the stimulus to renin secretion is still controversial and of much interest. Goldblatt[32] and those who followed him in this field, at first believed hypertension from renal artery compression was due to renal ischemia. "Ischemia" is apparently used here to mean a deficit of blood supply relative to the work done. Considerable evidence suggests that this view is incorrect. Dock and Rytand[33] using the method of partial nephrectomy in rats showed that the renal stump of a rat made hypertensive by this method did not carry less blood per gram of renal tissue. A large arterio-venous oxygen difference is generally regarded as a characteristic of ischemia. No change has been shown in the arterio-venous oxygen difference of the "ischemic" kidney.[34] This is not conclusive evidence, however, that the blood supply is enough; there might be insufficiency of some substance other than oxygen. Corcoran and Page,[35] using clearance methods, showed that some hypertensive Goldblatt animals did not have a diminished renal blood flow.

On this evidence we may accept for the present the concept that there may be some factor other than ischemia concerned with producing these changes. After Page[36] had demonstrated that a similar hypertension followed the perinephritis which developed around a kidney wrapped with silk or cellophane, the question arose, "Does this perinephritic capsule restrict the blood flow?" The answer to this is now known to be "Not always."[35]

Kohlstaedt and Page[37] demonstrated the liberation of renin by a kidney which was perfused with a pump-lung preparation. With the pulse pressure occurring in their circuit, they found no renin in the blood leaving the kidney. When they applied a clamp to the hose taking blood to the kidney, renin was promptly liberated in measurable amounts even though the blood flow through the kidney was not al-

lowed to diminish. This very important experiment has not received the enthusiastic acceptance it might deserve because of the obvious possibilities for error in so complicated a procedure. The methods for assay of renin in blood, still lamentably unsatisfactory, were at that time open to very grave doubt. The pulse-wave form and pulse pressure of a pump-lung preparation are determined by the specifications of the glass and rubber and are of evident importance in these experiments, but it is difficult to reproduce the experimental conditions exactly. Nevertheless, it seems reasonably certain that the principal change associated with the liberation of renin in this experiment was, in fact, a change in pulse pressure.

The concept that pulse pressure rather than ischemia determines the liberation of renin is of great importance. Since it was originally based on experiments involving so much technical skill and difficulty that nobody has yet repeated them, I may mention some other experiments which bear indirectly on this point. The importance of these experiments was not recognized since they were performed long before the recent revival of interest in renal hypertension.

A number of years ago I had the privilege of helping Dr. Bayliss[38] with a perfusion of some dog kidneys in a study of renal excretory mechanism. For convenience in the perfusion circuit we were using a high speed rotary pump[39] which gave about 800 pulsations per minute. In this circuit the pulse pressure must have been exceedingly small. Difficulty was experienced in forcing enough blood through the kidneys at a reasonable pressure, partly because of the well-known vasoconstrictor properties which shed blood may acquire, and partly, maybe, because of the liberation of renin by perfusion at a very low pulse pressure. We later found that the same circuit, equipped with a reciprocating pump giving approximately physiological pulse rate and pulse pressure, would allow adequate perfusion.

Many of the experiments demonstrating renin in the blood of the whole animal in response to what are usually spoken of as "hypotensive" stimuli further bear out the concept that the pulse pressure is the determining factor in the liberation of renin, though none of these experiments seems to provide critical evidence on this point.

The question therefore arises, can perinephritis affect the pulse pressure of the blood delivered to the kidney? This would be difficult to determine experimentally and no measurements have yet been re-

ported. Theoretical considerations suggest that if the kidney is rigidly splinted by experimental encapsulation the pulse pressure within it would be unchanged or might be somewhat increased though the magnitude of this increase would probably be negligible. It is unlikely that the kidney can distend and collapse to its normal degree with systole and diastole if it is encased in a rigid capsule. This would also be true if the pulse pressure delivered to a normal kidney (without perinephritis) were too small to produce the normal degree of expansile pulsation.

It appears that whenever renin is liberated the dynamic situation is such that the expansile pulsation of the kidney is diminished, but no critical experiments have yet been reported to prove a causal relationship even though this seems to be the only single relationship which will account for the generally accepted facts.

At the risk of theorizing on an imperfect foundation we may point to the facts that there are other organs which depend upon rhythmical movement for their well-being and that the elimination of tissue fluid, particularly by way of the lymphatics, is largely dependent upon physical movement of the organ concerned. Such factors might conceivably be concerned with the liberation of renin.

Space does not allow a detailed account of all the work which has been quoted for and against the view that the production of renin is a defense mechanism against blood volume deficit. It is sufficient if this account directs attention to the possibility that the kidney may be important in a certain group of cardiovascular emergencies.

The Posterior Lobe of the Pituitary Gland: A common emergency is that of water shortage which is met in part by the posterior lobe of the pituitary gland from which may be extracted a chemical, vasopressin (Pitressin), whose actions are three-fold. Vasopressin excites most smooth muscle in the body, it contracts capillaries and it promotes the reabsorption of water by the distal uriniferous tubule thus producing an antidiuretic effect.

Studying the antidiuretic properties of vasopressin, Gilman and Goodman[40] have shown that shortage of water is an appropriate stimulus to the liberation of this substance. They found that the rate of excretion of antidiuretic hormone in the urine was greater in those rats which had been dehydrated by lack of water or by hypertonic saline than in those which had been hydrated by the administration of excess water. It is evident that in such circumstances when the need for water

conservation is important this same substance is useful in its ability to mobilize blood by the constriction of capillaries and veins of the cutaneous and splanchnic areas.

The first activity of this substance to be recognized was its power to raise the blood pressure of anesthetized animals by peripheral arteriolar and capillary constriction. Thus it received its name "vasopressin." A careful study of its antidiuretic properties, however, has shown that this substance will produce antidiuretic effects in quantities far too small to have any detectable effect upon the blood pressure. For this reason there has been some question whether its blood pressure raising effect has any physiological significance and, in fact, Gilman and Goodman and others have even questioned whether injection of vasopressin raises the blood pressure of normal, unanesthetized man. However, after a careful consideration of the effects, Van Dyke[41] in his monograph of 1939 agrees with Schockaert and Lambillon[42] and others who claim that vasopressin injected intravenously will raise the blood pressure in man. This difference of opinion serves to emphasize the fact that the pressor activity is comparatively weak and therefore difficult to study.

Since the pressor action can be demonstrated, it is necessary to inquire whether it is a pharmacological accident or whether the effect occurs when the gland *in situ* is activated naturally. Excitation of the central end of the cut vagus can produce a sufficient liberation of posterior pituitary hormone to raise the blood pressure[43] but the proper physiological excitation of the vago-hypophyseal reflex has not yet been accomplished. The pressor activity of the pituitary gland may nevertheless be as physiological as its antidiuretic activity. If this be so, vasopressin acts not on one organ (the kidney) but on a variety of organs whose functions may be coördinated to meet the common emergency of water shortage. Vasoconstriction and antidiuresis would both serve the same end. This regulation of a single function of one substance which acts on a variety of mechanisms seems to be characteristic of the endocrine system.

The Adrenal Medulla: The recognition of the adrenal medulla as an endocrine organ for mobilizing all available resources for "fight or flight" was clearly established by the well-known work of Cannon.[44]

Violent excitation releases epinephrine which mobilizes blood by contraction of the spleen and the mesenteric veins. This action empties about a liter of cell-rich blood into the general circulation.[45] By con-

traction of the vessels in the plexuses of the skin another 500 cc. or so of blood is forced into the general circulation. And, finally, contraction of the splanchnic and cutaneous arterioles diverts the circulation from these regions to others of greater activity helping to maintain or raise the blood pressure by increasing the peripheral resistance. The increased blood volume tends to raise the venous pressure and distend the heart thereby raising the cardiac output and further helping to maintain the blood pressure. This is achieved in spite of an increasing demand for blood which is associated with widespread arterial relaxation in active parts of the body. The increased flow through the muscles still further adds to the venous return. That the venous pressure does not become inordinately high in these circumstances is due in part to three further actions of epinephrine. It acts on the pacemaker of the heart, increasing the rate and thus the number of rapid-filling periods per minute; secondly, it acts in a positive inotropic fashion,[46] increasing the power of a well-filled heart to empty itself rapidly and completely against a high blood pressure; and thirdly, it dilates the coronary arteries[47] and provides more oxygen for a hard-working heart.

In this way epinephrine not only increases the load of the heart but also increases its power to carry the load. The enormous increase in pulmonary blood flow[48] (approximately nine-fold) which occurs in these circumstances tends to produce a very high pulmonary arterial pressure. The pulmonary vessels, only lightly supported by the spongy parenchyma of the lungs, distend in response to this pressure and so more easily permit the increased quantity of blood to pass. The excessive distention of the pulmonary vessels, which might lead to rupture, is in part counteracted by the fact that epinephrine decreases their distensibility.[49]

This brief review of a few of the cardiovascular effects of epinephrine could be extended by a discussion of its possible effects on the aorta and the arteries within skeletal muscle, on the respiratory tract, and on metabolism and digestion. All these well-known actions of epinephrine support the concept that the adrenal medulla, like other endocrine glands, produces a secretion which helps to meet certain general situations rather than a substance specialized to act on any particular kind of tissue. The clearest cases in point are its widely differing action on the arterial muscle in the heart and in the gut, and the contrast between its inhibitory action on the digestive glands and its secretagogue action on the sweat glands.

The general concept of the emergency action of epinephrine has long been current. This has tended to obscure the fact that it is but one of the endocrine mechanisms organized to meet but one kind of emergency. The endocrine mechanisms for other emergencies have been studied more recently and less completely.

The Adrenal Cortex: A word must be said about the adrenal cortex as a cardiovascular organizer against stress on salt and water metabolism. Detailed information is accumulating so rapidly that no immediate attempt should be made to analyze this function rationally. However, the following simple points will bear pondering. The importance of the proper activity of the adrenal cortex in maintaining normal cardiovascular function is clearly shown by the diminished blood volume and lowered blood pressure in Addison's disease and perhaps also by the hypertension of Cushing's syndrome. The exact mechanisms involved are not clearly understood, nor is the nature of the environmental situations which led to their development.

The low blood pressure of adrenalectomized animals can be raised by the injection of desoxycorticosterone.[50] This substance controls the distribution of sodium and potassium, and secondarily, the volume and viscosity of the blood and the mechanical power of muscle including the heart. Whether these factors are the sole means by which the adrenal cortex controls the blood pressure is uncertain but in adrenal insufficiency the renin mechanism for blood pressure control is also abnormal.

A loss of renin substrate is found in adrenal insufficiency.[51] In animals with adrenal insufficiency administration of desoxycorticosterone restored the plasma substrate and blood pressure,[52] the vascular aspect of the mineral and fluid disturbance being counteracted by this endocrine mechanism. Whether salt shortage can evoke the activity of this adrenal mechanism, including the renin substrate changes, is a question which has not yet been answered by experiment. Here again, as in the case of the post-pituitary mechanisms, we are uncertain as to the true correlation of the various related functions such as sodium excretion, potassium mobilization, loss of tissue potassium, hemoconcentration and blood pressure.

The alarm reaction described by Selye[53] and others may well be the key to the part played by the adrenocortical mechanisms in cardiovascular regulation. In brief, Selye's observations show that violent

trauma and other stimuli producing shock, result in immediate cellular changes in the adrenal and lymphatic systems and in the production of edema. Teleologically speaking, shocking injuries are the prime occasions for increased formation of tissue fluid and at the same time necessitate the mobilization of the maximum blood volume. That the lymphatic system and the adrenal cortex with its salt regulating and protein regulating effects should play a part in the defense against such traumata is only to be expected. To date, our knowledge of this mechanism is somewhat deficient with respect to the involvement of physiological and biochemical phenomena but the edema discussed in Selye's report suggests that in these circumstances the reabsorption of tissue fluid is unable to keep up with its emergency production.

Though evidence is still incomplete we can discern four general situations which are met by four overlapping humoral mechanisms. These are shock and hypotensive emergencies met by renin, water shortage met by vasopressin, physical danger or violent somatic activity by epinephrine, and stress on salt metabolism by adrenocortical hormone.

The emergency of special effort, and epinephrine's part in the adjustment to it, are closely defined. It can be anticipated that with added knowledge, the nature of the other three situations will be defined more accurately than I have here been able to define them. Quite possibly other situations, each with its adjunct hormone, will emerge.

The Role of the Involuntary Nervous System

Attention has been unduly focused on the details of cardiovascular reflexes since there is no broad generalization to form a framework for their interpretation. The cardiovascular proprioceptive reflexes, organized in the medulla, are concerned with insuring the compatibility of simultaneously occurring cardiovascular events and thus averting the breakdown of the cardiovascular system itself.

These medullary cardiovascular reactions are not usually directed to the coördination between cardiovascular activities and the interests, activities, and safety of the organism as a whole, except in so far as these latter are dependent on the maintenance of an adequate coronary, and perhaps cerebral circulation. For example, the Bainbridge or accelerator reflex coördinates the frequency of the heart beat with the rate of venous inflow thus insuring that the heart may adjust its work output in an orderly fashion both by beating more often and by expelling

more blood per beat. Closely allied medullary reflexes affect the heart's metabolism enabling it to liberate more energy, and that more efficiently, in circumstances where it does more work. At the same time Anrep's coronary dilating reflex assures the heart of a blood supply adequate to meet an increased demand.

In somewhat similar fashion the moderator reflexes from the aortic arch and carotid sinuses seem designed, in part at least, to guard the pressure and diastolic time available for the coronary flow when a rising blood pressure or systolic output is throwing a big load on the heart. At the same time these vasosensory zones guard the internal carotid blood supply and thus protect the cardiovascular system against the fatal disaster of medullary ischemia and perhaps cerebral compression.

The Role of the Higher Nervous System

The self-regulatory mechanism consisting of the heart, great blood vessels, and medulla is controlled by nerve impulses coming down to it from higher levels of the brain. The full analysis of this control is complex and incomplete but it seems to be in the hypothalamus that the combined nervous and endocrine integration orders the relations between the cardiovascular system and the sometimes conflicting interests which it serves. Here also seems to lie the integration of the metabolic, emotional, intellectual and exteroceptive factors which make varying demands on the cardiovascular system.

Unsatisfactory coördination at this level may well be responsible for the complex psychosomatic syndromes arising when anxiety states cause a dominance of one organ system's activities over that of others.

In a few cases, apparently, fairly well integrated voluntary control can be exerted through these various levels to different parts of the cardiovascular system. Thus reports have been published of voluntary cardiac arrest,[54] of voluntary pulse acceleration,[55] and local vasoconstriction and vasodilatation.

Enough has been said to indicate the possibility that by thinking along the lines of the analysis suggested it may be possible to reduce a large amount of miscellaneous cardiovascular information to a simple and more comprehensible form.

Summary

An analysis of available knowledge of cardiovascular physiology

suggests that this information may be reduced to a simple and comprehensible form which may be summarized as follows:

The cardiovascular system like other body systems has such a physical and chemical make-up that the proper performance of its function is largely inherent. The activity of each tissue provides the chemical means of increasing its own blood supply.

The cardiovascular activities (and other activities, too) of many parts of the body are integrated and coördinated by the endocrine mechanisms to meet certain classes of emergency.

The heart, medulla, and cardio-medullary reflexes constitute a unit to maintain the integrity of the blood supply drained from the aorta in response to metabolite production and endocrine activity.

The higher parts of the brain provide rapid initiating adjustments whereby the cardiovascular system may be adjusted to new situations of exteroceptive, intellectual or emotional origin.

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THE EXCRETION OF STRONG ELECTROLYTES*†

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OUR knowledge of the mechanism of the tubular reabsorption of electrolytes has until recently been practically nil. The problem has seemed to present many complications. That there would be mutual interference in the reabsorption of electrolytes was anticipated, first, from the necessity of maintaining osmotic equality between the proximal tubular urine and the plasma, and second, because the essential feature of electrolyte control has seemed to be the maintenance of total base, which in turn is distributed in some specified manner between the two chief anions, chloride and bicarbonate. Furthermore, the data on chloride and bicarbonate reabsorption in the frog, Necturus,[1] rat and guinea pig[2] obtained by micropuncture studies, revealed that the reabsorption of chloride was certainly, and that of bicarbonate was probably distributed between the proximal and distal tubules, and there was *a priori* reason to suspect that these proximal and distal processes were fundamentally different in nature and subject to different types of control. Hence the task of describing electrolyte excretion quantitatively does not promise to be a simple one.

An effective start in this problem has, however, been made by Pitts and Lotspeich[3] in their study of the excretion of bicarbonate. Examination of the relations between the plasma bicarbonate concentration and bicarbonate excretion in the dog shows that the renal threshold for excretion is approximately 25 mM. per liter; below this level, essentially all the filtered bicarbonate is reabsorbed; above this level, the rate of excretion is roughly a linear function of the plasma concentration. This would be the result if the renal tubules reabsorbed filtered water and bicarbonate in the proportions of 25 mM. per liter, and rejected all

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filtered bicarbonate in excess of this. Since the quantity of water excreted from the glomerular filtrate is relatively small, as a first approximation it would be expected that "bicarbonate reabsorption per liter of glomerular filtrate" would remain fixed at the value of 25 mM. at all levels of bicarbonate above the threshold. Pitts and Lotspeich present data purporting to demonstrate this constancy in various animals under various experimental conditions.

Accepting for the moment the constancy of the above relationship, it must be noted that the mathematical operation of factoring data on any aspect of renal function by the filtration rate has three implications. First, it tends to eliminate simultaneous errors in the two terms attributable to errors in the timing or collection of urine samples. Second, it tends to eliminate differences, as between different individuals, in renal size, since in general various aspects of renal function in different animals show a rough correlation with the filtration rate, a correlation attributable to morphologic balance between glomerular and tubular function. Such a correlation between filtration rate and the maximal rate of reabsorption of glucose (glucose Tm) is not so evident in the dog because of marked changes in filtration rate associated with the dietary regime,[4] but the correlation is evident in man,[5] and a high degree of correlation between filtration rate and the maximal rate of tubular excretion of diodrast[6] and p-aminohippuric acid[7] has been clearly demonstrated in man. Assuming that a high degree of correlation exists between the filtration rate and the tubular capacity to reabsorb bicarbonate, attributable only to morphologic balance, then factoring bicarbonate reabsorption by filtration rate will tend to reduce the differences between different animals. There is, however, a third and more important implication in this factoring operation, namely, that bicarbonate reabsorption may be *functionally* related to the filtration rate in any one animal. This can only be established by showing that reabsorption increases or decreases with filtration rate in a single animal where, we may presume, the morphologic contribution of the tubules will remain constant despite variation in filtration rate. Pitts and Lotspeich's data seem to establish that this is actually the case with bicarbonate, since as the filtration rate increases in any one dog the rate of reabsorption of bicarbonate increases in a proportional manner. Glucose Tm in the dog and man, and sulfate[8] and phosphate[9] Tm in the dog are apparently determined by absolute limitations in the tubular transport mechanism

and are not influenced in any one individual by variations in the filtration rate. A situation where the rate of reabsorption is functionally related to the filtration rate in all physiological ranges requires a new interpretation.

In explaining this phenomenon, Pitts and Lotspeich start from the premise that roughly 80 per cent of the water of the glomerular filtrate is reabsorbed in the proximal tubule, regardless of the absolute filtration rate. They posit that the concentration of bicarbonate in this reabsorbate is *limited to a value of not more* than 25 mM. per liter. Secondly, they posit that in the distal system bicarbonate reabsorption is limited to a maximal rate of 0.5 mM. per minute, a figure based on a dog of such size as to have a filtration rate of 100 cc. but one which is independent of the actual filtration rate. In the Pitts-Lotspeich hypothesis we thus have two tubular maxima, a *concentration* maximum in the proximal reabsorbate, this reabsorbate amounting in volume to 80 per cent of the glomerular filtrate, and an absolute maximum in the distal system which is independent of the filtration rate.*

Pitts and Lotspeich suppose that when the plasma level of bicarbonate is 25 mM. per liter or less, 80 per cent of the filtered bicarbonate is reabsorbed in the proximal reabsorbate while the 20 per cent which is passed to the distal tubule is reabsorbed in the process of acidifying the urine. On elevation of the plasma bicarbonate above 25 mM. per liter, all bicarbonate in excess of this concentration is rejected in the proximal tubule and this moiety, together with that 20 per cent which normally is not reabsorbed, is passed to the distal system where quantities from zero up to 0.5 mM., depending on the activity of the acidifying mechanism, will be reabsorbed. Any excess over the sum of proximal reabsorption plus distal reabsorption will be excreted in the urine. Frank excretion of bicarbonate will begin when the total reabsorption amounts to approximately 25 mM. per liter of glomerular filtrate formed, and hence the system will operate to maintain the plasma level at 25 mM. per liter. Since proximal reabsorption is four times as great as distal reabsorption, total reabsorption will vary in rough proportion to the filtration rate no matter what the concentration-reabsorption relation in the distal process may be.

The hypothesis advanced by Pitts and Lotspeich, that a fluid of

* Distal reabsorption is related to the acidification of the urine, a process which has been explored in an exemplary manner by Pitts and Alexander,[10] but one which need not concern us here. The proximal reabsorptive process, on the other hand, is isohydric in that bicarbonate is reabsorbed as such without change in the H+ ion concentration of the tubular urine.

constant composition in respect to bicarbonate is reabsorbed in the proximal tubule, is an ingenious one, but it presents a serious philosophic difficulty. The authors carefully record the qualification that, "How the concentration of bicarbonate in the proximal reabsorbate is limited to 2.5 millimols per 100 cc. (of reabsorbate) is beyond our present comprehension." Were it necessary, which it is not, this qualification would relieve them of any criticism in what is said below. They do, however, note as a matter of history that the reabsorption of a fluid of constant composition with respect to bicarbonate recalls Cushny's concept that the tubular reabsorbate has an optimal composition in respect to many constituents (resembling Locke's solution). It is perhaps unfair to criticize Cushny's choice of words in speaking of the reabsorption of a *fluid* of optimal composition since quantitative concepts had not developed in Cushny's time to a point where one could ask for specific details as to how such an operation might be carried out. We must, however, ask the question now.

How can the tubules reabsorb a fluid of constant (or maximal) composition with respect to bicarbonate? Do the tubule cells reach out with a Maxwellian hand and scoop in a microscopic droplet of tubular urine containing exactly 25 mM. of sodium bicarbonate per liter, squeezing out the excess bicarbonate between its Maxwellian fingers before returning this ideal fluid to the plasma? Not only must the excess bicarbonate be squeezed out, but also all the urea, creatinine, inulin, etc. not reabsorbed by the renal tubules, all chloride, phosphate, sulfate, glucose, creatine, etc., in excess of reabsorption, and all the substances which are excreted by the renal tubules and not reabsorbed—these substances must be excluded or included with quantitative precision if all the requirements of tubular reabsorption and excretion are to be met. It would seem that the reabsorption of a *fluid* of specified composition with respect to bicarbonate, or with respect to any other solute, is a deceptive verbal trap. We need not look for Maxwellian fingers to *count* the number of bicarbonate ions per unit volume of water (i.e., the *concentration per se*) either in the tubular urine or in the tubule cell, but it would seem to require Maxwellian ingenuity to *separate* bicarbonate ions simultaneously with the requisite number of water molecules from all other species admixt therewith in the tubular urine, without either picking out bicarbonate ions and water molecules *individually*, or by absorbing tubular urine *en masse* and then re-excreting

all the undesirable constituents. To quote a criticism of Cushny's ideal fluid theory written ten years ago: "It is open to question if the hypothesis of the tubular reabsorption of a fluid of optimal composition is really a simplification. In order that the tubules may reabsorb a fluid of optimal composition containing a large number of chemical substances in different concentration, there would seemingly be required just as elaborate physical-chemical apparatus as for them to reabsorb each of these constituents separately and independently."[11] So we return to the alternative interpretation, that what the tubules really do is to absorb bicarbonate ions and water molecules *separately* and *independently*, though perhaps in such proportions that the net result is as though they reabsorbed a solution of constant composition with respect to these constituents.

Is it conceivable that the proximal tubule can reabsorb water molecules "separately and independently," without reference to anything else? The distal tubule apparently does this when it abstracts water molecules from a mixture of sodium chloride, urea, creatinine, and other solutes, and, by reducing the water content of the residual urine, raises its osmotic pressure to several times that of the blood. So long as it is permissible to suppose that the distal tubule actively reabsorbs water molecules *per se* in making a hypertonic urine, we cannot dismiss the possibility in the proximal tubule.

We are, however, not forced to believe that the proximal reabsorption of water is necessarily an active and independent process: it may be a wholly passive one. As sodium (with its attendant chloride and bicarbonate) is reabsorbed the osmotic pressure of the tubular urine tends to be reduced and, if the proximal tubule is significantly permeable to water, water may simply diffuse back into the plasma to maintain the osmotic U/P ratio close to unity. In this view, a liter of water would be passively reabsorbed for each 145 mM. of sodium reabsorbed, and the net effect would to all appearances be the reabsorption of a fluid of constant composition. This sequence would follow the reabsorption of glucose, amino acids, phosphate and all other constituents of the tubular urine—in each case the precise osmotic equivalent of water would follow the reabsorbed solute back into the blood, without specific intervention on the part of the tubule. For simplicity, the passive reabsorption of water in the proximal tubule presents a very attractive hypothesis.

If the proximal reabsorption of water is a matter of passive diffusion, one might expect the proximal tubular urine to be at times at least slightly hypotonic to the blood. Walker, Bott, Oliver and MacDowell[2] obtained a hypotonic urine from the proximal tubule of the rat in only two out of twenty-one instances, but their observations were made on unilaterally nephrectomized animals which were generally loaded with sucrose or saline, both of which circumstances may have increased the filtration rate per nephron and altered the conditions of proximal reabsorption. Or perhaps in the normal animal the movement of water is so rapid that osmotic equilibration is almost instantaneous. In any case, the available data do not exclude the passive diffusion hypothesis.

Lotspeich, Swan and Pitts[12] have presented a limited examination of chloride excretion in the dog. As in the case of bicarbonate, the quantity of chloride reabsorbed is directly proportional to the filtration rate, not only in different animals but in the same animal, at the rate of 115 mM. per liter.*

Additional evidence of this functional relationship can be derived from data in the literature. The reabsorption of chloride in dogs receiving various saline infusions has been described by Hare, Hare and Phillips.[13] These authors did not examine their results from the present point of view, but recalculation of their data shows that in any one dog the chloride reabsorbed per unit of glomerular filtrate is remarkably constant, regardless of marked changes in filtration rate resulting from the administration of saline, and despite the administration of large doses of antidiuretic hormone. The mean rate of reabsorption in the data of Hare, Hare and Phillips is 111 mM. per liter, as compared with 115 mM. per liter in the data presented by Lotspeich, Swan and Pitts on acidotic dogs. Barclay and Cooke[14] have recognized the above relationship in the data of Hare *et al,* but offer no interpretations in terms of renal mechanism.

Mokotoff, Ross and Leiter[15] have similarly found that in normal subjects and subjects in heart failure (in some of the latter the filtration rate is extremely low) the quantity of sodium reabsorbed varies directly as the filtration rate, reabsorption being in the proportion of 133 mM. for each liter of filtrate formed. This relationship is also evident in the data of Talbott, Pecora, Melville and Consolazio[16] on sodium reabsorption in patients with Addison's disease and pan-hypopituitarism.

In looking at the over-all aspects of sodium (or chloride) reabsorption, too much emphasis must not be placed on the high degree of correlation between the quantity reabsorbed and the filtration rate. A gross linear relationship inevitably issues by definition if the urinary excretion of sodium is small: the equation appropriate to the excretion of any substance which is completely filterable but subsequently reabsorbed by the tubules (neglecting the Donnan equilibrium) is

(1) $PC_f = T + UV$

* The reabsorption of chloride must be conditioned by the reabsorption of bicarbonate, and *vice versa,* since these anions are extensively interchangeable in the plasma, and, as demonstrated by Pitts and Lotspeich, elevation of plasma chloride decreases the reabsorption of bicarbonate and *vice versa.* It is not known how the reabsorption of one anion conditions the reabsorption of the other.

where P is the plasma concentration in mg. per cc., C_t the filtration rate in cc. per minute, T is the quantity reabsorbed and UV the quantity excreted, both in mg. per minute. Dividing by C_t,

$$(2)\quad P = T/C_t + UV/C_t$$

If UV is zero or negligibly small, T will vary directly as C_t, the slope of the curve T vs. C_t (or the ratio of the two terms) being equal to P. It so happens that UV seldom exceeds 20 per cent of T and is generally less, while P is nearly constant in all individuals; hence when T is plotted against C_t it has a high linear correlation, with only small deviations attributable to variations in P and UV.

Thus the above correlation only expresses the fact that sodium (or chloride) and water will be reabsorbed in some constant proportion as a formal consequence of equation (2) so long as the absolute quantities of both substances excreted are but small fractions of the quantities filtered. What is required is to discover the determinants which govern the small deviations from this formal relationship when P or C_t are varied independently.

Stimulated by the Pitts-Lotspeich hypothesis for bicarbonate reabsorption, we have examined [17] the reabsorption of sodium and water in the dog, first, in respect to whether these processes are intrinsically dependent or whether sodium can be reabsorbed independently of water; and second, as to whether the urine formed in the proximal system is or is not invariably isotonic with the plasma, i.e., whether water is reabsorbed in the quantity required by the passive diffusion hypothesis.

Osmotic diuresis was induced by infusion of 25 per cent mannitol solution at approximately 0.8 cc. per kg. per minute in trained, unanesthetized dogs. The filtration rate was measured by the creatinine clearance and sodium, chloride, bicarbonate and mannitol were determined in plasma and urine by standard methods.

When the concentration of mannitol in the plasma (and hence in the glomerular filtrate) is raised to substantial levels the mannitol retards by its osmotic pressure the reabsorption of water in the proximal system, and increasing quantities of water are delivered to the distal system, exceeding the reabsorptive capacity of the latter and resulting in marked increases in urine flow (osmotic diuresis). Under such conditions a large fraction of the water of the glomerular filtrate may be

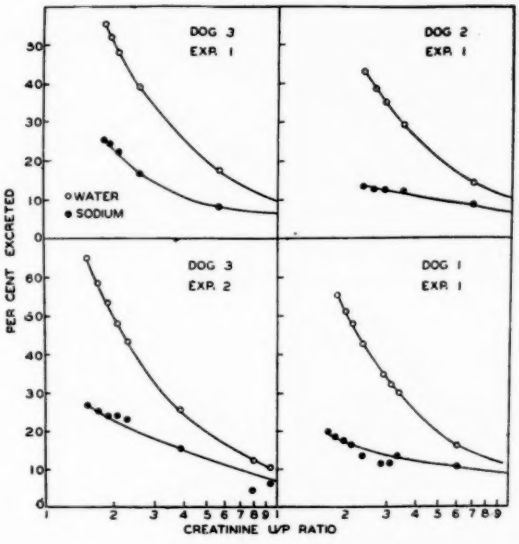

Fig. 1. The relative fraction of filtered sodium and water excreted in the urine during progressive osmotic diuresis induced in the dog by the intravenous administration of mannitol. The sequence of urine collection periods begins at the right and moves progressively to the lower creatinine U/P ratios as the diuresis increases in magnitude.

The mannitol sweeps much more water than sodium into the urine, indicating that sodium reabsorption is an active process which is only slightly disturbed by the conditions of the experiment.

excreted in the urine and the creatinine U/P ratio may be reduced to low values.[18]

Four such experiments are shown in Figure 1. It will be seen that it is possible to sweep out as much as 65 per cent of the filtered water while sweeping out only 13 to 27 per cent of the filtered sodium. A fifth experiment, not illustrated here, gave similar results.* The data will not be recorded here, but in these experiments chloride followed sodium, as might be expected. Bicarbonate excretion remained small even at large urine flows. These experiments demonstrate that the reabsorption of sodium is operationally independent of the reabsorption of

* Schou[19, 20] has shown that during sulfate diuresis in the rabbit, a relatively small fraction of the filtered chloride is excreted despite the excretion of a considerable fraction of the filtered water.

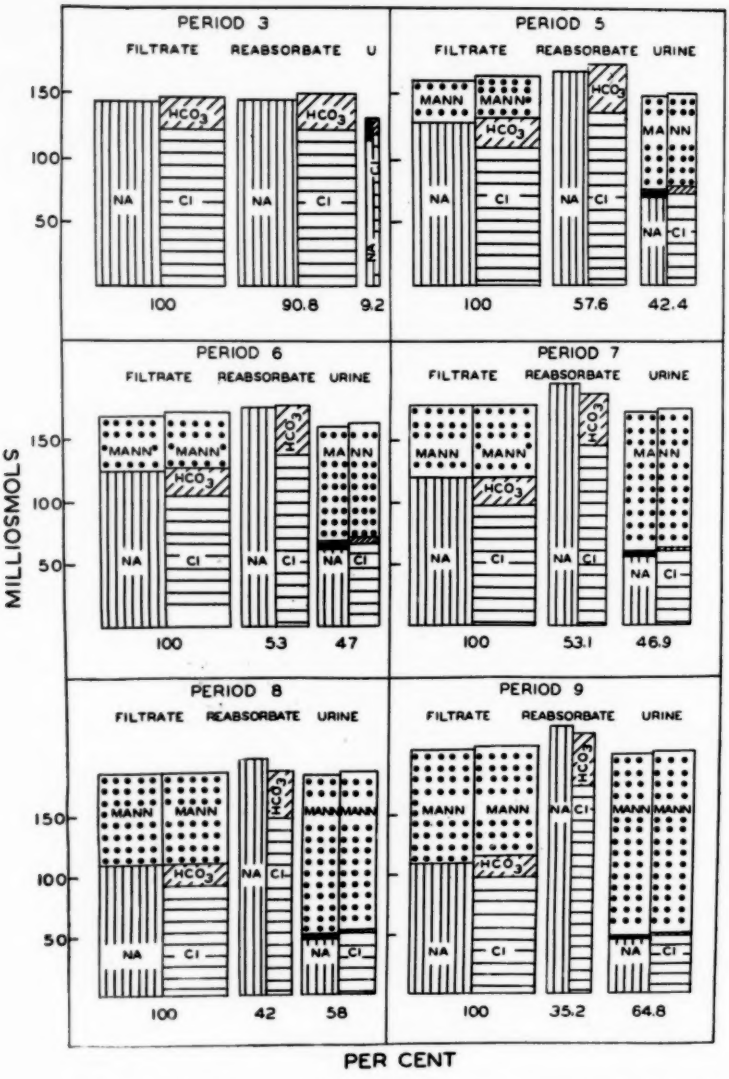

Fig. 2. Six urine collection periods from an experiment in which progressively increasing osmotic diuresis was induced in a dog by mannitol. The osmotic constituents of the filtrate (left) urine (right) and the total reabsorbate (center) as calculated by difference, are plotted in terms of milliosmols. (K is shown in solid black). The figures below the blocks show the relative volumes of filtrate, reabsorbate and urine formed per minute, the volume of filtrate in each instance being taken as 100.

As the plasma concentration of mannitol rises, this substance contributes an increasing fraction to the osmotic pressure of the plasma and urine. The three fluids remain, however, essentially isotonic, indicating that the fluid delivered to the distal tubule is itself isotonic with the plasma.

water, and that any interpretation involving the reabsorption of an "ideal fluid" or one of "optimal" composition must be abandoned.

Calculations based upon the above experiments also demonstrate, we believe, that the proximal reabsorbate is in general isotonic with the plasma. Evidence has been presented that under normal conditions some 85 per cent of the filtered sodium and water are reabsorbed proximally;[21] although the final composition of the urine is specifically determined by the operations of the distal tubule, the net operation of the latter upon the fate of the glomerular filtrate as a whole is small. Under conditions of substantial osmotic diuresis, the quantity of proximal urine delivered to the distal tubule is so great that the specific operations of the latter, normally small in absolute magnitude, are swamped in the flood, so to speak, and the composition of the urine must come to reflect closely the composition of the fluid delivered to the distal tubule by the proximal system.

Figure 2 shows the detailed data on six urine collection periods in an experiment with mannitol diuresis. This experiment is one of five which have given the same results. In the experiment illustrated a 25 per cent solution of mannitol was infused at the rate of 1.1 cc. per kg. per minute. The plasma mannitol concentration rose from zero in period 3 to 3070 mg. per cent in period 9, the urine flow increasing from 4.6 to 31.5 cc. per minute and the creatinine U/P ratio falling from 11.5 to 1.62. When we add up the osmotic constituents of the plasma, on the one hand, and of the urine, on the other,* we find that within the limits of experimental error the osmotic pressure of the urine remains equal to that of the plasma, despite the fact that in the latter part of the experiment mannitol supplies a large fraction of the osmotic pressure of both fluids. Since the urine is simply what is left over after the abstraction of the reabsorbate, it follows that the reabsorbate itself has throughout the experiment remained isosmotic with this plasma. This evidence merely confirms, in a sense, the observations of Walker, Bott, Oliver and MacDowell[2] in the rat and guinea pig, but the observations of these investigators were of necessity confined to the first half of the proximal tubule; our present data extend the principle of isosmotic reabsorption† to the over-all proximal operations in the kidney

* No allowance has been made for the reabsorption up to 10 per cent of mannitol, as recently reported by Berger, Farber and Earle.[22]

† We use the terms isosmotic reabsorption and reabsorbate only to indicate the over-all operation and without implication that the reabsorption of sodium and water occur simultaneously at any one point in the proximal tubule.

of the dog, and under much more drastic conditions than obtained in the experiments of the Long Island investigators.

We are then in a position to say that although the proximal reabsorption of sodium and water are operationally independent processes, they proceed in such a manner that the proximal urine (and hence the proximal reabsorbate) remains in general closely isosmotic with the plasma.** This is consonant with the view, suggested above, that the reabsorption of sodium is an active process and that water passively diffuses back through the proximal tubule and thin limb under the resulting osmotic gradient.†‡

This view affords an attractive explanation of the function of the thin segment of the loop of Henle. The older idea, that because this segment occurs only in the Classes (birds and mammals) where ADH promotes water reabsorption, it is the locus of the formation of a concentrated urine and of osmotic work, has never had strong appeal because its flat epithelium does not, by contrast with the distal tubule, seem cytologically constituted for such a function. Our present interpretation would be identical with that of Shannon,[23] who some years ago proposed that the thin limb serves to promote osmotic equilibration by passive diffusion of water between tubular urine and plasma after the bulk of the sodium, etc., has been reabsorbed proximally.§ We would interpret the coincidence of the evolution of the thin limb and of the activity of ADH in promoting water reabsorption (which we refer to the distal tubule) as an adaptation facilitating reduction to a minimum of the water load delivered to the distal tubule where final water and sodium reabsorption must be effected. To deliver a variable excess of fluid to this terminal segment would conceivably be disadvantageous to its precise operations in the critical retention of sodium and water, especially where these two functions are themselves possibly sharply limited by critical constants.

The above conclusions lay the foundations for a more detailed ex-

** More correctly, of course, one should refer to the renal interstitial fluid rahter than plasma, but for brevity we will consider the interstitial fluid as invariably isosmotic with the plasma.

† This statement should be qualified to the extent that conditions can be conceived where the proximal urine may be hypotonic to the plasma. Such conditions will be considered in a subsequent paper.

‡ We cannot positively exclude the possibility that *active* reabsorption of water may proceed independently of sodium reabsorption in such a manner as to maintain an isosmotic reabsorbate, but this interpretation requires that the active process be limited by an osmotic U/P ratio of 1.0, which as matters stand would leave us with no evidence for such an active process.

§ Shannon supposed, incorrectly we now believe, that all the sodium was reabsorbed in the proximal system and that a very dilute urine, equivalent to that obtained during water diuresis, was delivered to the distal tubule.

ploration of sodium and water reabsorption. Nominally, we are required to consider four processes, proximal sodium and water reabsorption, and distal sodium and water reabsorption. Since, under conditions of isosmotic reabsorption, the relative quantities of sodium and water in the proximal reabsorbate are contingent on the osmotic composition of the plasma, which is, of course, available to measurement, only one of the remaining terms must be determined in order to afford a quantitative description of both proximal and distal operations.

That some sodium is reabsorbed by the distal tubule is demonstrated in the frog and *Necturus* by the data on chloride of Walker, Hudson, Findley and Richards,[1] and there is at least an implication that this is the case in the data of Walker *et al*[2] on the rat. These studies show that a significant reabsorption of water occurs below the proximal tubule, presumably in the distal tubule,* but the actual volume of water reabsorbed distally is unknown. Ever since the recognition of the functional difference between obligatory and facultative water reabsorption,[21] the latter has been attributed to the distal tubule, which would mean that this segment normally receives about 15 per cent of the glomerular filtrate for reabsorption.

That the distal reabsorption of sodium and water are operationally independent of each other must be accepted so long as the distal tubule is accepted to be the locus of facultative water reabsorption. This facultative process may vary from some substantial value to zero, depending on the presence or absence of ADH; and this variation is not accompanied by a commensurate variation in sodium excretion. Indeed, there is no evidence that the latter is subject to analogous "facultative" control. (We do not overlook the possible significance of abrupt changes in the secretion of adrenocortical hormones).

We therefore accept that about one-eighth of the water of the glomerular filtrate is delivered to the distal tubule for facultative reabsorption. So long as the proximal fluid remains isosmotic with the plasma, it follows that an equal fraction of the filtered sodium also reaches the distal tubule where it is largely reabsorbed, since far less than this amount is customarily excreted. What is of chief interest to

* It would perhaps be consonant with all available facts to attribute facultative water reabsorption to the thin limb (it could be supposed that ADH promotes the passive diffusion of water in this segment, or even in the proximal tubule) but at least one circumstance argues against this interpretation. The fraction of the glomercular filtrate (*ca.* one-eighth) available for water diuresis is relatively independent of the absolute value of the filtration rate;[24] this constancy seems difficult to explain if the water of water diuresis represents a residue which has simply failed to diffuse back in the proximal system in the absence of ADH.

us at the moment is the upper limits of distal reabsorption of water and sodium.

It has been noted that systems involving tubular transport have with few exceptions been demonstrated to be limited by maximal rates—or at least by rates which do not change beyond the limits of experimental error with increasing load once the load has exceeded some critical value. In general these "maximal rates" of tubular transport are at least roughly reproducible in any one animal under basal conditions. Whether these liminal phenomena issue from limitations in available energy or limitations in the enzymatic transfer system need not concern us now. Distal reabsorption of water, unlike proximal reabsorption, appears to be an active process comparable with other active tubular transport systems, and as such it might be anticipated *a priori* that the absolute quantity of water per unit time would also have some upper, limiting value in cc. per minute. We may designate this supposed maximal rate as $T^dm_{H_2O}$, using Tm in the general sense of a limiting value in any tubular transport system and T^d to indicate specific reference to the distal tubule. $T^dm_{H_2O}$ may be substantially larger than the load of water normally delivered to the distal tubule. Similarly we may designate the maximal rate of sodium reabsorption in the distal tubule as T^dm_{Na}, emphasizing that neither of these supposed constants has as yet received adequate experimental verification. $T^dm_{H_2O}$ and T^dm_{Na} would of course only be reached if the distal load of water or sodium, respectively, were equal to or exceeded the maximal reabsorptive capacity for either substance, and $T^dm_{H_2O}$ would be reached only if the reabsorptive process were maximally activated by ADH. At partial states of ADH activation distal water reabsorption ($T^d_{H_2O}$) would be less than $T^dm_{H_2O}$, and, in the absence of ADH, might decrease to zero.

The experimental demonstration of these suppositious constants is obviously complicated by such variables as the absolute magnitude of the filtration rate from moment to moment, the variable endogenous secretion of ADH, and, at least during oliguria, by the maximal osmotic pressure of the urine,* as well as by a possible velocity effect which, during osmotic diuresis, may operate against osmotic equilibration in the proximal system.

* The lower limit of urine flow when the distal load is less than Tdm_{H_2O} is doubtless determined by the osmotic ceiling against which the distal tubule can concentrate the urine.

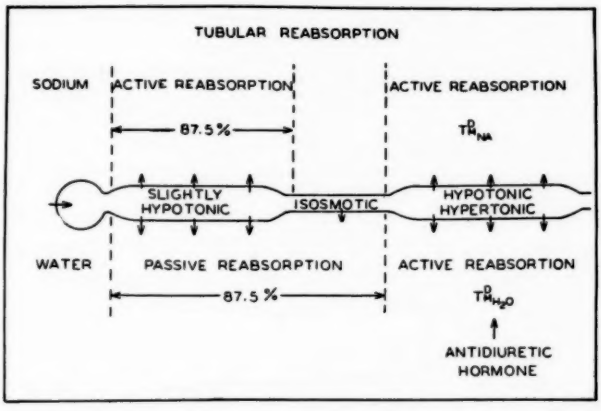

Fig. 3. In the hypothesis presented in this paper it is presumed that sodium with chloride and bicarbonate is reabsorbed in the proximal tubule by an active process, leading to the formation of a slightly hypotonic urine. In consequence of this hypotonicity water diffuses back into the plasma so that a fluid essentially isotonic with plasma is delivered to the distal tubule. It is conceived that the function of the thin limb is to promote osmotic equilibration. Reabsorption in the proximal tubule and thin limb accounts for roughly seven-eighths of the glomerular filtrate, leaving one-eighth to be operated upon in the distal tubule.

It is believed that water and sodium are actively but independently reabsorbed in the distal tubule by processes which are limited by maximal rates ($T^{d}m_{H_2O}$ and $T^{d}m_{Na}$. The distal reabsorption of water is activated by the antidiuretic hormone which, with the osmoreceptors of the supraopticohypophyseal system, comprises the mechanism for the control of water equilibrium.

We have for some time been engaged in the intensive investigation of this problem, but we have been unable as yet to demonstrate the stability of these constants under a variety of conditions, possibly because of the above complicating factors, and possibly because our hypothesis is oversimplified.** However, we believe the hypothesis will be useful in guiding experimental work and in visualizing over-all renal function in the maintenance of salt and water balance (See Figure 3).

Since $T^{d}_{H_2O}$ can vary from zero to $T^{d}m_{H_2O}$ in consequence of variations in ADH secretion, water equilibrium will be maintained

** We have evidence of an hysteresis-like phenomenon, whereby maximal water and sodium reabsorption increase gradually during the course of several hours following a sudden increase in filtration rate, despite a constant filtered load. This may reflect variable endocrine activity induced by sodium administration or adaptive changes in the tubules themselves.

despite marked variations in the filtration rate, except under conditions of osmotic diuresis when the water load exceeds $T^d m_{H_2O}$ or distal reabsorption is opposed by the diuretic agent. This is equivalent to saying that at all times the sodium concentration of the plasma will be regulated to a critical value through the supraopticohypophyseal system by the retention or rejection of water.

So long as the fraction of filtered sodium reabsorbed proximally remains approximately constant, or does not vary through too wide a range, the load of sodium delivered to the distal tubule will increase or decrease with the filtration rate. At some critical filtration rate this load will be exactly equal to $T^d m_{Na}$ and the subject will be exactly in sodium equilibrium. If the filtration rate is increased the distal load will be increased and come to exceed $T^d m_{Na}$, leading to the excretion of the excess sodium. Where sodium is excreted more rapidly than water, the sodium content of the plasma will decrease and this reduction of osmotic pressure, acting through the supraopticohypophyseal system, will lead to the distal rejection of water until the critical osmotic pressure of the plasma is restored.

Conversely, if the filtration rate is reduced, the distal load of sodium will be less than $T^d m_{Na}$ and sodium reabsorption will be essentially complete. Where sodium reabsorption exceeds water reabsorption, the ultimate increase in the osmotic pressure of the plasma, operating through the supraopticohypophyseal system, will increase the distal reabsorption of water until the critical osmotic pressure of the plasma is restored.

At a given plasma concentration of sodium there will be one and only one filtration rate at which the subject will remain exactly in sodium equilibrium. It will be convenient to refer to this filtration rate as the equilibrium filtration rate.

Fluctuations in the filtration rate above or below the equilibrium filtration rate may be of considerable importance in sodium balance. It is common knowledge that the oral administration of moderate doses of isotonic saline (ex. one liter in a man) does not result in an abrupt excretion of fluid, as does the administration of an equal volume of water. The saline is excreted slowly and may not be recovered for a number of hours. On absorption of the saline no change occurs in the osmotic pressure of the plasma and one wonders why the saline is excreted. It has recently been recognized that one method of increasing

the filtration rate consistently in the dog, and this is possibly true in man, is the administration of saline. The increase in filtration rate after the rapid intravenous administration of saline occurs more slowly and outlasts by a considerable period the sojourn of the saline in the vascular tree, as indicated by dilution of the plasma proteins or reduction in hematocrit.[25] It appears probable that the increase in filtration rate increases the load of sodium to the distal tubule until this exceeds T^{a}_{mNa}, when the excess sodium is excreted. Plasma dilution results and, through the supraopticohypophyseal system, the excess water is ultimately excreted. The slowness with which glomerular activity is adjusted may explain the slowness with which saline diuresis is initiated, and the relatively small increase in the filtration rate at the peak of diuresis may be responsible for the relatively slight magnitude of the diuresis.

Conversely, after the withdrawal of plasma (isotonic fluid) from the body, its restoration is effected in a relatively short time. Extreme hemorrhage and shock[26-30] are accompanied by a marked reduction in filtration rate and it is quite possible that a reduction of small but significant magnitude may occur after moderate blood loss. A similar cycle of events might operate to conserve salt and water under conditions of excessive sweating, vomiting, diarrhea, etc.

It will be noted that in all these operations only very small changes in filtration rate need be involved. In a man with a plasma sodium concentration of 138 mM. per liter and a filtration rate of 130 cc. per minute, a decrease or increase of filtration rate of only some 6 cc. per minute would be required to retain or excrete 15 gm. of sodium per day, if proximal reabsorption continues to account for 80 per cent of the filtered sodium. Variations of this order are scarcely beyond the experimental error of our present methods of clinical investigation. Moreover, nearly all our available data are based upon short period observations, whereas in the maintenance of sodium equilibrium, we are of course concerned with glomerular activity as distributed over the entire 24 hour period, and it is highly probable that this activity is influenced by meals, posture, exercise, sleep and possibly many other factors.

By coupling together the renal mechanism controlling the excretion of sodium, the supraopticohypophyseal mechanism for controlling the excretion of water, and the glomerular apparatus controlling the filtra-

tion rate, we would have an integrated system that will not only regulate the composition of the extracellular fluid, but its volume as well. The above considerations lead us to inquire whether there exists in the body a mechanism by which expansion or contraction of the extracellular fluid compartment tends automatically to increase or decrease the filtration rate. The existence of such a mechanism seems highly probable, but we know nothing about it at the present time, nor do we have any certain knowledge of how, within the glomerular apparatus itself, changes in filtration rate are effected.* We are certain that these changes cannot be accounted for solely on the basis of plasma dilution. A most important field lies open here for investigation. Further progress in this problem requires an adaptation of the clearance technique to studies extending over a period of 24 hours or longer, whereby some of these factors may be studied.

A single clinical application of the above hypothesis will be useful. Seymour, Pritchard, Longley and Hayman,[31] and more recently Merrill[32] have reported that the renal blood flow and filtration rate are reduced in chronic congestive heart failure, the latter to one-half or one-third of the normal. Merrill attributes the continued, complete reabsorption of sodium to the reduction in the amount of sodium filtered in consequence of the reduced filtration rate, an interpretation which is in accord with our hypothesis. When the filtered load of sodium is reduced, the load delivered to the distal tubule is less than $T^{d}mNa$ and sodium reabsorption is essentially complete. Through the supraopticohypophyseal system water is retained in characteristic proportions to sodium, and isotonic edema fluid accumulates in the body. Interruption of this cycle requires the restoration of the filtration rate to normal, reduction of the sodium intake, or reduction in sodium reabsorption by a mercurial diuretic.

Mokotoff, Ross and Leiter[15] have confirmed Merrill's observation that the filtration rate is reduced in cardiac failure, and demonstrated further that this reduction is not due to neurogenic vasoconstriction: in only one of 11 instances did the filtration rate increase during high

* A unique and interesting implication of the above considerations is that a 'steady state' cannot be achieved by the progressive, uniform excretion of excess sodium in accordance with renal clearance principles, since an infinite time would be required to reach equilibrium; it appears that this difficulty is resolved in this as in other physiological systems (the regulation of respiration, blood pressure, body temperature, etc.) by over-compensation and hence oscillation above and below the steady state as a mean. In its long-range operation the above system will cause the filtration rate to oscillate above and below the equilibrium value, and the plasma sodium concentration to oscillate above and below a mean value determined by the critical, osmotic threshold of the supraopticohypophyseal system, damping in respect to both sodium and water retention being effected by the critical renal barriers $TmdNa$ and Tmd_{H_2O}.

spinal anesthesia in patients in whom the blood pressure was maintained with ephedrine.[33] Farnsworth[34] also reports low filtration rates in some patients in failure, but in others the data fall within the normal range. Merrill's suggestion conforms, as said above, with our present knowledge of renal function, but it remains to be determined that this is the only and necessary condition for salt and water retention. The general absence of edema in hypertension and frequent absence in chronic diffuse glomerulonephritis, where the filtration rate may be markedly reduced, seems to require either that nephrons are destroyed in a nearly unitary manner in these diseases, maintaining glomerular-tubular balance in the functional parenchyma, or that other factors may be operating in cardiac failure.

Merrill considers the reduced filtration rate in cardiac failure to be a concomitant of renal ischemia, the renal blood flow being reduced in favor of more vital parts of the circulation, as in hemorrhage and shock. He believes that the decreased renal blood flow is attributable to the secretion of renin, which he and his colleagues have demonstrated to be present in the renal venous blood during cardiac decompensation.[32] Whatever the agent, it may be suspected that it reflects a disturbance of the mechanism, the existence of which is suggested above, whereby glomerular activity is adjusted to the volume of the extracellular fluid.

The studies of Brod[35] indicate that in normal subjects the filtration rate, as judged roughly by the clearance of endogenous creatinine-like chromogen, increases during the morning and decreases at night, particularly during sleep. It is well known[36, 37] that the urine flow and electrolyte excretion tend to follow this diurnal pattern, though the physiological basis is obscure. The change in urine flow is possibly related to a change in filtration rate or possibly to a diurnal pattern in ADH secretion. In some patients with congestive heart failure, the above pattern is reversed, and Brod has shown that the nocturia is associated with a marked increase in the endogenous creatinine chromogen clearance, indicating that it is related to an increase in filtration rate. Workers in this laboratory have noted that in subjects with essential hypertension, nocturia when present may be associated with a significant increase in eudogenous creatinine clearance and chloride excretion, suggesting that the filtration rate is fluctuating close to the equilibrium level required for saturation of the distal tubule with respect to sodium. The cycle, although not consistently present, suggests some close rela-

tionship between sleep and control of the glomerular apparatus.

Future studies of electrolyte and water balance must take cognizance of such long-range changes, recognizing the principle that the kidneys, functionally poised in glomerular-tubular balance, the extracellular fluid, the vascular tree, and the heart, constitute a system the integration of which is essential not only to salt and water balance, but also to the efficiency of the circulation.

Summary

Recent investigations have shown that the tubular reabsorption of electrolytes (bicarbonate, chloride and sodium) is functionally related to the filtration rate, presumably because an approximately constant fraction (*ca* seven-eighths) of the filtered sodium and water are reabsorbed by the proximal tubule and thin limb, regardless of the filtration rate.

During osmotic diuresis induced by the intravenous infusion of hypertonic mannitol solution in the dog, the fraction of water reabsorbed proximally is substantially reduced and large quantities of fluid are delivered to the distal tubule. However, the fraction of sodium reabsorbed proximally is not reduced commensurately. Thus, as much as 65 per cent of the water of the glomerular filtrate may be excreted in the urine at a time when only 13 to 27 per cent of the filtered sodium is being excreted. On this basis it is believed the reabsorption of sodium by the renal tubules is operationally independent of the reabsorption of water.

Under these conditions the composition of the urine is believed to represent with close approximation the composition of the urine at the end of the thin limb. Since, during osmotic diuresis, the osmotic pressure of the urine closely approaches the osmotic pressure of the plasma, it follows that the proximal reabsorbate is itself isosmotic with the plasma. It is inferred that this isosmotic relationship obtains under ordinary conditions. This concept is consonant with the view that proximal reabsorption of sodium is an active process and that under the resulting osmotic gradient water passively diffuses back through the proximal tubule and thin limb to maintain an isosmotic relation.

The "facultative" reabsorption of water, representing about one-eighth of the water of the glomerular filtrate, is believed to be a function of the distal tubule. In view of the evidence that the urine delivered

from the proximal tubule is isosmotic with plasma, it follows that an additional fraction of sodium is reabsorbed distally. It is suggested that the distal reabsorption of sodium and water are independently limited by maximal rates of tubular transport, such as have been demonstrated in other tubular transport systems.

These concepts of electrolyte excretion are discussed in relation to the excretion of isotonic saline, the retention of sodium and water in hemorrhage, shock and related conditions of dehydration, to edema formation in cardiac failure, and to diurnal variations in the excretion of electrolytes and water.

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EDEMA OF HEART FAILURE*

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PROBLEMS related to the mechanism of cardiac edema have appealed to the clinician and physiologist alike because of the abundance of material available for study. The edema fluid is readily obtained by pricking the skin, and the techniques for studying the venous pressure and other aspects of the circulation have been highly developed.

Our original approach to the problem was the analysis of the protein content of the edema fluid.[1] Fluid obtained from the skin and subcutaneous tissues of patients with congestive failure contains little protein. This fact alone indicates that the primary mechanism of cardiac edema can be neither lymphatic obstruction nor increased capillary permeability. The finding is compatible, however, with hypoproteinemia, or increased venous pressure, or retention of fluid by the kidney.

Since the plasma protein concentration is normal in many patients, hypoproteinemia can be eliminated as the primary factor in cardiac edema. A moderate increase in venous pressure produces edema which contains relatively little protein. The same type of low-protein edema results from the administration of physiologic saline solution at a rate greater than the capacity of the kidneys to excrete fluid. Examination of the fluid alone did not distinguish between these mechanisms. This finding led to additional observations on the relationship between plasma volume and edema fluid. In chronic congestive failure, the plasma volume is elevated and the protein content of the edema fluid is low. In normal subjects the venous pressure in a large part of the body may be increased by motionless standing. This uniformly produces a fall in plasma volume, as fluid is forced through the capillaries by the high hydrostatic pressure. The decrease in volume may be corrected in part by drinking several liters of physiologic saline solution, but even with persistent drinking the plasma volume falls. As urine flow practically ceases, body weight increases. These observations suggested that

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the edema of congestive failure might not be due to an elevated systemic venous pressure because the edema of congestive failure is associated with an increased blood volume. Fluid given to a normal subject lying horizontal at a rate greater than can be excreted by the kidney causes a large blood volume and edema fluid low in protein. This combination is present in acute nephritis,[2] pregnancy, and congestive failure. These cumulative data suggest that the primary mechanism of cardiac edema is related to the fact that the fluid intake exceeds the fluid output, and that a disturbance in renal function produced by heart failure may be the primary cause of cardiac edema.

Because of the emphasis usually placed on the causative role of an elevated venous pressure in the edema of heart failure, the relationship between the venous pressure and cardiac edema was examined at greater length. It was obvious that in many subjects, edema persisted long after the venous pressure returned to normal and that in others edema returned without a corresponding rise in venous pressure. Observations on patients with superior mediastinal obstruction or patients with inferior caval ligation showed that a change in venous pressure of the magnitude seen in early congestive failure did not produce the massive edema so characteristic of heart failure. Warren and I examined the sequence of events in two patients who had been made edema-free by salt restriction and the administration of mercurial diuretics.[3] Both patients formed edema on a high salt intake. The edema and an increase in plasma volume preceded any measurable rise in venous pressure, indicating that the elevated venous pressure was not the cause of retention of fluid but was, instead, secondary to it.

On rigid sodium restriction, patients with congestive failure tolerate water remarkably well, but the addition to the diet of a small amount of sodium will cause swelling. These data pointed to the primary retention of sodium with resultant retention of water. The role of chloride, also, appeared to be a secondary one, because the administration of $NaHCO_3$ caused edema while NH_4Cl did not.

The problem now resolved itself into a study of the mechanism by which sodium was retained when the heart failed. A study of the hemodynamics of the kidney in congestive failure seemed a logical step. A preliminary survey of the literature, however, was discouraging, and a few random studies in our laboratory demonstrated that though renal function was highly abnormal in certain patients with congestive fail-

ure, it was normal in others. After a time, we realized that these differences existed because the circulatory state of our patients varied. One group of patients will develop congestive failure during their usual activity, but will have adequate circulations at rest. Observations on such patients show normal resting cardiac outputs, normal renal blood flows, and normal responses to added salt in diet. These circulatory measurements may be normal in the presence of edema because it takes time to complete a diuresis. Obviously, the mechanism of edema formation at rest could not be studied in such patients whose resting circulation was adequate. In contrast, however, certain patients become edematous at rest whenever they are placed on a normal diet. They become edema-free only when the intake of sodium is sharply restricted or after the repeated administration of mercurial diuretics. This latter group who formed edema at rest was selected for the study of the mechanism of edema formation.

The data on cardiac output in patients selected on this basis are of interest.[4] The basal cardiac output as related to the surface area of the body is nearly always lower than in normal subjects. As the oxygen consumption is within normal limits unless the subject is uncomfortable or dyspneic, this means that the arteriovenous oxygen difference is greater than normal. The marked disturbance of the pumping ability of the heart is magnified by light exercise. There are certain exceptions to the observation that failure is accompanied by an absolute lowering of the resting cardiac output. In patients who are restless and uncomfortable and in those with anemia or thyrotoxicosis, failure may occur in the presence of a cardiac output above the normal resting level. It should be noted that an elevated cardiac output is characteristic of patients with similar physiologic or pathologic disturbances who have no heart failure. It is not surprising, therefore, that when the circulation becomes inadequate they develop the signs of circulatory insufficiency before their outputs fall to the normal level. In summary, the observations on cardiac output indicate that the signs of congestive failure develop whenever the cardiac output is inadequate for the body needs over a prolonged period of time. The absolute value at which the cardiac output becomes inadequate will depend on the needs of the body for blood. In myxedema, the level will be low; in anemia and hyperthyroidism, high.

Merrill studied the renal blood flow and filtration rate in this group

of patients who formed edema at rest.[5] He found the renal blood flow to be reduced to ⅓ to ⅕ of the normal value, and the filtration rate to be reduced to ½ to ⅓ of normal. The filtration fraction was increased. The renal arteriovenous oxygen difference was increased. The extraction of PAH by the kidney was normal.

The fall in filtration rate resulted in a marked reduction in the amount of sodium filtered. The tubules reabsorbed almost entirely the greatly reduced amount of sodium presented to them. Even so, in absolute terms, they reabsorbed much less sodium than normal subjects under similar conditions. It appears that one of the functions of the tubular cells is to reabsorb sodium, and that the cardiac patient has no mechanism to depress this function to a level which will allow the sodium to leave the kidney. Therapeutically, of course, we solve this difficulty by temporarily poisoning the cells with an organic mercurial preparation. It is true that many situations exist in which the filtration rate is lowered without the development of edema. In a patient with Addison's disease, the filtration rate is lowered and sodium is still excreted in spite of the falling blood level. In this instance, disturbances in tubular function because of adrenal insufficiency over-balance the decrease in filtration rate. In chronic glomerular nephritis, the filtration rate is lowered. If the tubular dysfunction is less severe than glomerular dysfunction, edema occurs; if tubular dysfunction is more severe, the patient develops a marked sodium deficiency on a low salt diet. If the tubular and glomerular lesions balance, neither edema nor dehydration develop. Cardiac failure is peculiar in that a profound disturbance in glomerular filtration occurs in the presence of a minimum of demonstrable tubular damage.

The high filtration fraction indicated that the reduction in renal blood flow was the primary cause of the reduced filtration rate. The question, then, resolved itself into an analysis of the factors reducing the renal blood flow. Merrill[5] presented data to show that the reduction in filtration rate and renal blood flow was not correlated with changes in right atrial pressure, but was related to changes in cardiac output. Throughout this talk, the term "inadequate cardiac output" has been used. We are now in a position to define this term more precisely as it relates to cardiac edema. The absolute level of cardiac output is of little importance. It is inadequate whenever for a long period of time too little blood is pumped to give the kidneys their normal share. The kid-

neys suffer early and to a greater extent than other organs when the blood supply is reduced. The mechanism of the fall in renal blood flow in the presence of an inadequate cardiac output has not been determined. Merrill[5] did demonstrate that the fall in renal blood flow was greater than the fall in output. A decreased renal blood flow occurs not only in chronic congestive failure, but in normal subjects on motionless standing or vigorous exercise and in patients in shock. It would be helpful if the exact time relationship were known. How long must the cardiac output be decreased before the renal blood flow falls? How long does it take the renal blood flow to rise after the cardiac output is increased?

Myers[6] has recently shown that the hepatic blood flow is low in chronic congestive failure. However, in contrast to the findings in the renal circulation, the fall in hepatic flow is proportional to the fall in output. The difference in the response of the renal and hepatic blood flows to the same stimuli is well shown in anemic patients without failure. In this instance, the hepatic blood flow is greatly increased,[7] while the renal flow is moderately reduced.[8]

While recent studies have emphasized the role of the kidney in cardiac edema, clinical observation has long demonstrated that many patients with heart failure have an elevated venous pressure. A rise in right atrial venous pressure may be accomplished in three ways: (1) increase in blood volume, (2) increase in vascular tone, and (3) shift of blood from the lesser to the greater circulation, or vice versa. In patients with chronic failure and a fixed low cardiac output, the venous pressure varies directly with blood volume.[2] In normal subjects, sympathico-mimetic drugs, such as paredrinol,[9] cause a rise in venous pressure without a rise in cardiac output; and plethysmographic observations on these subjects demonstrate a rise in venous tone. Clinical observations suggest that any sharp reduction in cardiac output below the body needs results in a rise in vascular tone unless neurogenic collapse occurs, or tissue necrosis or infection is extensive.[10] If the blood volume is reduced, as in hemorrhage, there is a rise in vascular tone without an elevation in venous pressure. If the blood volume is increased, or normal, as in heart failure, a rise in vascular tone is accompanied by a rise in venous pressure. The sudden fall in venous pressure which occurs after digitalization may be the result of a change in venous tone. Whether this is a direct effect of digitalis or secondary to the rise in

cardiac output has not been determined.

The shifts of blood from the lungs to the general circulation have not been studied in heart failure. As left ventricular failure is the common situation, usually blood from the peripheral circulation is accumulating in the lungs. If, however, the situation is reversed and right ventricular failure predominates, the blood available for backing up behind the right heart is that which is pumped by the right heart to the left heart plus the blood which can be delivered to the left heart by constriction of the pulmonary vascular tree. It is doubtful if enough blood is ever mobilized from the lungs by constriction to produce an appreciable rise in the systemic venous pressure unless venous constriction in the peripheral bed occurs at the same time.

Reichsman and Grant[11] have shown that certain patients with mitral stenosis and auricular fibrillation who are digitalized will have a rise in venous pressure if the digitalis is omitted. This fits in with our observations. Unfortunately, it does not help to solve the problem of edema because it is probable that in these patients the rise in venous pressure is coincident with a fall in cardiac output. We are then left with the fact that either variable, the reduction in cardiac output or the rise in venous pressure, might be responsible for initiating the chain of events leading to gross edema.

Changes in capillary pressure and in tissue pressure are extremely important in determining the deposition of the fluid retained by the kidneys. If physiologic saline solution is given to a subject who is leaning motionless against a wall, the fluid will accumulate in the lower part of the body because of the high capillary pressure. If he lies down, the fluid will have to be given at a much more rapid rate to exceed the rate of excretion by the kidneys. It will be more evenly distributed and will first become visible as puffiness about the eyes. In the loose periorbital tissue, a large amount of fluid may accumulate without an increase in tissue pressure.

The effect of a rise in venous pressure on the distribution of salt and water may be illustrated by a patient whose inferior vena cava had been ligated for recurrent pulmonary emboli. The brachial venous pressure was 60 mm. of water, and the femoral, 200 mm. On a low salt diet, there was no pitting edema. On a high salt diet, the patient gained weight and developed pitting edema of the lower half of the body. Similarly. patients with low grade venous obstruction may have very

little edema until the onset of congestive failure. Then massive edema of the obstructed part may occur before considerable edema is demonstrable elsewhere.

It is at once obvious that patients with heart failure differ from normal subjects in the way they handle fluid when the intake exceeds the output. The patient with failure tends to store a large amount of fluid in the lungs, and massive pulmonary edema may precede any detectable signs of peripheral edema. In congestive failure, the pulmonary arterial pressure is elevated.[12] If a portion of this rise in resistance is a reflection of high left atrial and pulmonary capillary pressures, we have a satisfactory answer for the predisposition to pulmonary edema in the patient with failure. While this assumption is supported by indirect evidence, direct measurement of the pulmonary venous pressure has not been made.

Use of mercurial diuretics and rigid restriction of sodium in the diet has modified our conception of cardiac decompensation. The symptoms of congestive heart failure can be divided into two large groups. The first group includes symptoms referable to poor function of tissues and organs caused by the inability of the heart to maintain the blood supply of the part. The muscular weakness of congestive failure falls into this class. The second group of symptoms is related to the accumulation of excess salt and water in the organs and tissues of the body. Dyspnea, orthopnea, and cough belong here. These symptoms which result from edema will disappear on rigid salt restriction even though the circulation has not improved. The dyspneic, orthopneic, miserable patient becomes a comfortable, normal-appearing ambulatory subject as long as sodium is withheld. The extent of symptomatic improvement in such a patient would lead one to say the heart was now compensated. Actually, the circulation may not have improved, and return to a normal diet may produce a recurrence of symptoms.

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